

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
21 May 2004 (21.05.2004)

PCT

(10) International Publication Number
WO 2004/041801 A1

(51) International Patent Classification⁷: **C07D 295/155**,
333/20, 307/52, 277/28, A61K 31/495, 31/496, A61P
25/04

KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT,
RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:

PCT/SE2003/001706

(22) International Filing Date:

5 November 2003 (05.11.2003)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

0203302-5 7 November 2002 (07.11.2002) SE

(71) Applicant (for all designated States except US): AS-
TRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BROWN, William**
[CA/CA]; AstraZeneca R & D Montreal, 7171 Freder-
ick-Banting, St. Laurent, Montreal, Québec H4S 1Z9
(CA). **GRIFFIN, Andrew** [GB/CA]; AstraZeneca R & D
Montreal, 7171 Frederick-Banting, St. Laurent, Montreal,
Québec H4S 1Z9 (CA).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; As-
traZeneca AB, S-151 85 Södertälje (SE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

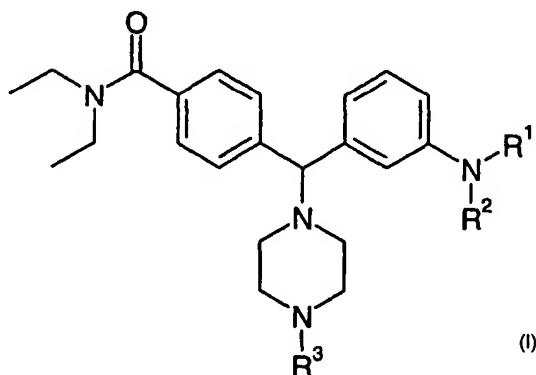
— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES,
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO
patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG,
ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT,
RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: 4(PHENYL-PIPERAZINYL-METHYL) BENZAMIDE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF PAIN OR GASTROINTESTINAL DISORDERS



(i)

(57) Abstract: Compounds of general formula: [Chemical formula should be inserted here. Please see paper copy] wherein R₁, R₂, and R₃ are as defined in the specification, as well as salts, enantiomers thereof and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the management of pain.

BEST AVAILABLE COPY

WO 2004/041801 A1

4(PHENYL-PIPERAZINYL-METHYL) BENZAMIDE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF PAIN OR GASTROINTESTINAL DISORDERS

BACKGROUND OF THE INVENTION

1. Field of the Invention

5 The present invention is directed to novel compounds, to a process for their preparation, their use and pharmaceutical compositions comprising the novel compounds. The novel compounds are useful in therapy, and in particular for the treatment of pain, anxiety and functional gastrointestinal disorders.

2. Discussion of Relevant Art

10 The δ receptor has been identified as having a role in many bodily functions such as circulatory and pain systems. Ligands for the δ receptor may therefore find potential use as analgesics, and/or as antihypertensive agents. Ligands for the δ receptor have also been shown to possess immunomodulatory activities.

15 The identification of at least three different populations of opioid receptors (μ , δ and κ) is now well established and all three are apparent in both central and peripheral nervous systems of many species including man. Analgesia has been observed in various animal models when one or more of these receptors has been activated.

20 With few exceptions, currently available selective opioid δ ligands are peptidic in nature and are unsuitable for administration by systemic routes. One example of a non-peptidic δ -agonist is SNC80 (Bilsky E.J. et al., Journal of Pharmacology and Experimental Therapeutics, 273(1), pp. 359-366 (1995)).

25 Many δ agonist compounds that have been identified in the prior art have many disadvantages in that they suffer from poor pharmacokinetics and are not analgesic when administered by systemic routes. Also, it has been documented that many of these δ agonist compounds show significant convulsive effects when administered systemically.

U.S. Patent No. 6,130,222 to Roberts et al. describes some δ -agonists.

However, there is still a need for improved δ -agonists.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless specified otherwise within this specification, the nomenclature used in
5 this specification generally follows the examples and rules stated in *Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H*, Pergamon Press, Oxford, 1979, which is incorporated by references herein for its exemplary chemical structure names and rules on naming chemical structures.

The term " C_{m-n} " or " C_{m-n} group" used alone or as a prefix, refers to any group
10 having m to n carbon atoms.

The term "hydrocarbon" used alone or as a suffix or prefix, refers to any structure comprising only carbon and hydrogen atoms up to 14 carbon atoms.

The term "hydrocarbon radical" or "hydrocarbyl" used alone or as a suffix or prefix, refers to any structure as a result of removing one or more hydrogens from a
15 hydrocarbon.

The term "alkyl" used alone or as a suffix or prefix, refers to monovalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms. An "alkyl" may optionally contain one or more unsaturated carbon-carbon bonds.

20 The term "alkylene" used alone or as suffix or prefix, refers to divalent straight or branched chain hydrocarbon radicals comprising 1 to about 12 carbon atoms, which serves to links two structures together.

The term "alkenyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon
25 double bond and comprising at least 2 up to about 12 carbon atoms.

The term "alkynyl" used alone or as suffix or prefix, refers to a monovalent straight or branched chain hydrocarbon radical having at least one carbon-carbon triple bond and comprising at least 2 up to about 12 carbon atoms.

The term "cycloalkyl," used alone or as suffix or prefix, refers to a
30 monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms.

The term "cycloalkenyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon double bond and comprising at least 3 up to about 12 carbon atoms.

5 The term "cycloalkynyl" used alone or as suffix or prefix, refers to a monovalent ring-containing hydrocarbon radical having at least one carbon-carbon triple bond and comprising about 7 up to about 12 carbon atoms.

The term "aryl" used alone or as suffix or prefix, refers to a monovalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, $4n + 2$ delocalized electrons) and comprising 5 up to about
10 14 carbon atoms.

The term "arylene" used alone or as suffix or prefix, refers to a divalent hydrocarbon radical having one or more polyunsaturated carbon rings having aromatic character, (*e.g.*, $4n + 2$ delocalized electrons) and comprising 5 up to about 14 carbon atoms, which serves to link two structures together.

15 The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may
20 contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings share two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

The term "heteroaromatic" used alone or as a suffix or prefix, refers to a ring-
25 containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s), wherein the ring-containing structure or molecule has an aromatic character (*e.g.*, $4n + 2$ delocalized electrons).

30 The term "heterocyclic group," "heterocyclic moiety," "heterocyclic," or "heterocyclo" used alone or as a suffix or prefix, refers to a radical derived from a heterocycle by removing one or more hydrogens therefrom.

The term "heterocyclyl" used alone or as a suffix or prefix, refers a monovalent radical derived from a heterocycle by removing one hydrogen therefrom.

The term "heterocyclylene" used alone or as a suffix or prefix, refers to a divalent radical derived from a heterocycle by removing two hydrogens therefrom,
5 which serves to links two structures together.

The term "heteroaryl" used alone or as a suffix or prefix, refers to a heterocyclyl having aromatic character.

The term "heterocyclcoalkyl" used alone or as a suffix or prefix, refers to a heterocyclyl that does not have aromatic character.

10 The term "heteroarylene" used alone or as a suffix or prefix, refers to a heterocyclylene having aromatic character.

The term "heterocycloalkylene" used alone or as a suffix or prefix, refers to a heterocyclylene that does not have aromatic character.

15 The term "six-membered" used as prefix refers to a group having a ring that contains six ring atoms.

The term "five-membered" used as prefix refers to a group having a ring that contains five ring atoms.

A five-membered ring heteroaryl is a heteroaryl with a ring having five ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

20 Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4- oxadiazolyl.

25 A six-membered ring heteroaryl is a heteroaryl with a ring having six ring atoms wherein 1, 2 or 3 ring atoms are independently selected from N, O and S.

Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

The term "substituted" used as a prefix refers to a structure, molecule or group, wherein one or more hydrogens are replaced with one or more
30 C₁₋₆hydrocarbon groups, or one or more chemical groups containing one or more heteroatoms selected from N, O, S, F, Cl, Br, I, and P. Exemplary chemical groups containing one or more heteroatoms include -NO₂, -OR, -Cl, -Br, -I, -F, -CF₃,

-C(=O)R, -C(=O)OH, -NH₂, -SH, -NHR, -NR₂, -SR, -SO₃H, -SO₂R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR₂, -NRC(=O)R, oxo (=O), imino (=NR), thio (=S), and oximino (=N-OR), wherein each "R" is a C₁₋₆hydrocarbaryl. For example, substituted phenyl may refer to nitrophenyl, methoxyphenyl, chlorophenyl, aminophenyl, etc.,
5 wherein the nitro, methoxy, chloro, and amino groups may replace any suitable hydrogen on the phenyl ring.

The term "substituted" used as a suffix of a first structure, molecule or group, followed by one or more names of chemical groups refers to a second structure, molecule or group, which is a result of replacing one or more hydrogens of the first
10 structure, molecule or group with the one or more named chemical groups. For example, a "phenyl substituted by nitro" refers to nitrophenyl.

Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-
15 dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihdropyran, tetrahydropyran, 1,4-dihdropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

20 In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4- oxadiazole.

25 Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine,
30 naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole,

benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Heterocyclyl includes, for example, monocyclic heterocyclyls, such as: aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, dioxolanyl, sulfolanyl, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl, tetrahydrofuranyl, thiophanyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, 2,3-dihydropyranyl, tetrahydropyranyl, 1,4-dihydropyridinyl, 1,4-dioxanyl, 1,3-dioxanyl, dioxanyl, homopiperidinyl, 2,3,4,7-tetrahydro-1*H*-azepinyl, homopiperazinyl, 1,3-dioxepanyl, 4,7-dihydro-1,3-dioxepinyl, and hexamethylene oxidyl.

In addition, heterocyclyl includes aromatic heterocyclyls or heteroaryl, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, furazanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl.

Additionally, heterocyclyl encompasses polycyclic heterocyclyls (including both aromatic or non-aromatic), for example, indolyl, indolinyl, isoindolinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,4-benzodioxanyl, coumarinyl, dihydrocoumarinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, isobenzofuranyl, chromenyl, chromanyl, isochromanyl, xanthenyl, phenoxathiinyl, thianthrenyl, indolizinyl, isoindolyl, indazolyl, purinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, phenanthridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 1,2-benzisoxazolyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benzimidazolyl, benztriazolyl, thioxanthinyl, carbazolyl, carbolinyl, acridinyl, pyrolizidinyl, and quinolizidinyl.

In addition to the polycyclic heterocyclyls described above, heterocyclyl includes polycyclic heterocyclyls wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidinyl, 5 diazabicyclo[2.2.1]heptyl; and 7-oxabicyclo[2.2.1]heptyl.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula $-O-R$, wherein R is selected from a hydrocarbon radical. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, isobutoxy, cyclopropylmethoxy, allyloxy, and propargyloxy.

10 The term "amine" or "amino" used alone or as a suffix or prefix, refers to radicals of the general formula $-NRR'$, wherein R and R' are independently selected from hydrogen or a hydrocarbon radical.

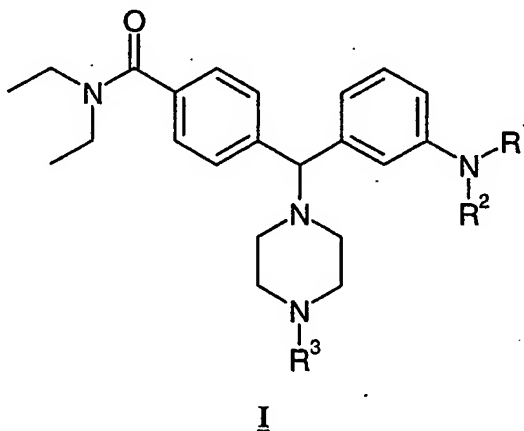
Halogen includes fluorine, chlorine, bromine and iodine.

"Halogenated," used as a prefix of a group, means one or more hydrogens on 15 the group is replaced with one or more halogens.

"RT" or "rt" means room temperature.

Description of Embodiments

In one aspect, the invention provides a compound of formula I, enantiomers 20 thereof, diastereomers thereof and pharmaceutically acceptable salts thereof:



wherein

R^1 is selected from C_{3-6} alkyl, C_{6-10} aryl, C_{2-9} heteroaryl, C_{6-10} aryl- C_{1-4} alkyl, C_{2-9} heteroaryl- C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, $R^8-C(=O)-$, $R^8-S(=O)_2-$, $R^8-S(=O)-$, $R^8-NHC(=O)-$, $R^8-C(=S)-$ and $R^8-NH-C(=S)-$, wherein R^8 is selected from C_{3-6} alkyl, C_{6-10} aryl, C_{2-9} heteroaryl, C_{6-10} aryl- C_{1-4} alkyl, C_{2-9} heteroaryl- C_{1-4} alkyl, C_{3-10} cycloalkyl, and C_{3-10} cycloalkyl- C_{1-4} alkyl, wherein said C_{3-6} alkyl, C_{6-10} aryl, C_{2-9} heteroaryl, C_{6-10} aryl- C_{1-4} alkyl, C_{2-9} heteroaryl- C_{1-4} alkyl, C_{3-10} cycloalkyl, and C_{3-10} cycloalkyl- C_{1-4} alkyl used in defining R^1 and R^8 are optionally substituted with one or more groups selected from -R, -NO₂, -OR, -Cl, -Br, -I, -F, -CF₃, -C(=O)R, -C(=O)OH, -NH₂, -SH, -NHR, -NR₂, -SR, -SO₃H, -SO₂R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR₂, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, selected from -H, C_{1-6} alkyl and phenyl;

R^2 is selected from -H and C_{1-6} alkyl optionally substituted with one or more groups selected from halogen, -CF₃, -OH, C_{1-3} alkoxy, and halogen; and

R^3 is selected from -H, C_{1-6} alkyl-O-C(=O)-, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl- C_{1-4} alkyl, wherein said C_{1-6} alkyl-O-C(=O)-, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl- C_{1-4} alkyl are optionally substituted with one or more groups selected from C_{1-6} alkyl, halogenated C_{1-6} alkyl, -NO₂, -CF₃, C_{1-6} alkoxy and halogen.

In one embodiment, the compounds of the present invention are represented by formula I, wherein

R^1 is selected from C_{3-6} alkyl, C_{6-10} aryl, C_{2-6} heteroaryl, C_{6-10} aryl- C_{1-4} alkyl, C_{2-6} heteroaryl- C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl, wherein said C_{3-6} alkyl, C_{6-10} aryl, C_{2-6} heteroaryl, C_{6-10} aryl- C_{1-4} alkyl, C_{2-6} heteroaryl- C_{1-4} alkyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkyl- C_{1-4} alkyl are optionally substituted with one or more groups selected from C_{1-4} alkyl, halogen, -CF₃, -OH, C_{1-3} alkoxy, phenoxy, and halogen;

R^2 is selected from -H and C_{1-3} alkyl; and

R^3 is selected from -H and C_{1-6} alkyl-O-C(=O)-.

In another embodiment, the compounds of the present invention are represented by formula I, wherein R^1 is R^9-CH_2- , wherein R^9 is selected from phenyl, pyridyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, thiazolyl, N-oxido-pyridyl, benzyl, pyridylmethyl, thienylmethyl, furylmethyl, imidazolylmethyl, triazolylmethyl, pyrrolylmethyl, thiazolylmethyl and N-oxido-pyridylmethyl, optionally substituted

with one or more groups selected from C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy and halogen; and

R² and R³ are hydrogen.

In another embodiment, the compounds of the present invention are
5 represented by formula I,

wherein R¹ is R⁹-CH₂-, wherein R⁹ is selected from benzyl, phenyl, pyridyl, thienyl, furyl, imidazolyl, pyrrolyl and thiazolyl, optionally substituted with one or more groups selected from C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy, and halogen; and

10 R² and R³ are hydrogen.

In another embodiment, the compounds of the present invention are represented by formula I, wherein

wherein R¹ is R⁹-CH₂-, wherein R⁹ is selected from benzyl, phenyl, pyridyl, thienyl, furyl, imidazolyl, pyrrolyl and thiazolyl; and

15 R² and R³ are hydrogen.

In another embodiment, the compounds of the present invention are represented by formula I, wherein

R¹ is selected from C₃₋₆alkyl, C₃₋₁₀cycloalkyl, and C₃₋₁₀cycloalkyl-C₁₋₄alkyl, wherein said C₃₋₆alkyl, C₃₋₁₀cycloalkyl, and C₃₋₁₀cycloalkyl-C₁₋₄alkyl are optionally
20 substituted with one or more groups selected from C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy, and halogen;

R² is -H or C₁₋₃alkyl; and

R³ is -H, C₁₋₆alkyl, C₃₋₆cycloalkyl, and C₃₋₆cycloalkyl-C₁₋₄alkyl, wherein said C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl are optionally substituted with one
25 or more groups selected from C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy, and halogen.

In another embodiment, the compounds of the present invention are represented by formula I, wherein

R¹ is selected from 1-propyl, 2-propyl, 1-butyl, 2-butyl, t-butyl, 2-methyl-1-propyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and cyclononyl;
30

R² is selected from -H, methyl, ethyl, 1-propyl and 2-propyl; and

R^3 is selected from -H, methyl, ethyl, allyl, 3,3-dimethyl-allyl, cyclopropylmethyl, 2-methoxy-ethyl, and 3-methoxy-1-propyl.

In another embodiment, the compounds of the present invention are represented by formula I, wherein

5 R^1 is selected from $R^8-C(=O)-$, $R^8-S(=O)_2-$, $R^8-S(=O)-$, $R^8-NHC(=O)-$, $R^8-C(=S)-$ and $R^8-NH-C(=S)-$, wherein R^8 is selected from C_{3-6} alkyl, C_{6-10} aryl, C_{2-6} heteroaryl, C_{6-10} aryl- C_{1-4} alkyl, C_{2-6} heteroaryl- C_{1-4} alkyl, C_{3-10} cycloalkyl, and C_{3-10} cycloalkyl- C_{1-4} alkyl; wherein said C_{3-6} alkyl, C_{6-10} aryl, C_{2-6} heteroaryl, C_{6-10} aryl- C_{1-4} alkyl, C_{2-6} heteroaryl- C_{1-4} alkyl, C_{3-10} cycloalkyl, and C_{3-10} cycloalkyl- C_{1-4} alkyl are
10 optionally substituted with C_{1-4} alkyl, halogen, $-CF_3$, $-OH$, C_{1-3} alkoxy, phenoxy, and halogen;

R^2 is -H; and

R^3 is selected from -H and C_{1-6} alkyl-O-C(=O)-.

In a further embodiment, the compounds of the present invention are
15 represented by formula I, wherein

R^1 is selected from $R^8-C(=O)-$, $R^8-S(=O)_2-$, $R^8-S(=O)-$, $R^8-NHC(=O)-$, $R^8-C(=S)-$ and $R^8-NH-C(=S)-$, wherein R^8 is selected from phenyl, benzyl, phenethyl and cyclohexyl, wherein said phenyl, benzyl, phenethyl and cyclohexyl are optionally substituted with one or more groups selected from methyl, methoxy and halogen;

20 R^2 is -H; and

R^3 is selected from -H and C_{1-6} alkyl-O-C(=O)-.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be
25 isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by
30 asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present

invention includes any geometrical isomer of a compound of Formula I. It will further be understood that the present invention encompasses tautomers of the compounds of the formula I.

It will also be understood that certain compounds of the present invention may
5 exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the formula I.

Within the scope of the invention are also salts of the compounds of the formula I. Generally, pharmaceutically acceptable salts of compounds of the present
10 invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a
15 compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

20 In one embodiment, the compound of formula I above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

The novel compounds of the present invention are useful in therapy, especially
25 for the treatment of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar
30 surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of opioid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson's disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following myocardial infarction, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of formula I, or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes
5 "prophylaxis" unless there are specific indications to the contrary. The term
"therapeutic" and "therapeutically" should be construed accordingly. The term
"therapy" within the context of the present invention further encompasses to
administer an effective amount of a compound of the present invention, to mitigate
either a pre-existing disease state, acute or chronic, or a recurring condition. This
10 definition also encompasses prophylactic therapies for prevention of recurring
conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for
the therapy of various pain conditions including, but not limited to: chronic pain,
neuropathic pain, acute pain, back pain, cancer pain, and visceral pain.

15 In use for therapy in a warm-blooded animal such as a human, the compound
of the invention may be administered in the form of a conventional pharmaceutical
composition by any route including orally, intramuscularly, subcutaneously, topically,
intranasally, intraperitoneally, intrathoracically, intravenously, epidurally,
intrathecally, intracerebroventricularly and by injection into the joints.

20 In one embodiment of the invention, the route of administration may be orally,
intravenously or intramuscularly.

The dosage will depend on the route of administration, the severity of the
disease, age and weight of the patient and other factors normally considered by the
attending physician, when determining the individual regimen and dosage level at the
25 most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this
invention, inert, pharmaceutically acceptable carriers can be either solid and liquid.
Solid form preparations include powders, tablets, dispersible granules, capsules,
cachets, and suppositories.

30 A solid carrier can be one or more substances, which may also act as diluents,
flavoring agents, solubilizers, lubricants, suspending agents, binders, or table
disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

5 For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized moulds and allowed to cool and solidify.

10 Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

15 The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

20 Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

25 Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

30 Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably

from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and
5 response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of formula I as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of formula I
10 for the manufacture of a medicament for the therapy of pain.

Additionally provided is the use of any compound according to Formula I for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: chronic pain, neuropathic pain, acute pain, back pain, cancer pain, and visceral pain.

15 A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I above, is administered to a patient in need of such therapy.

Additionally, there is provided a pharmaceutical composition comprising a
20 compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

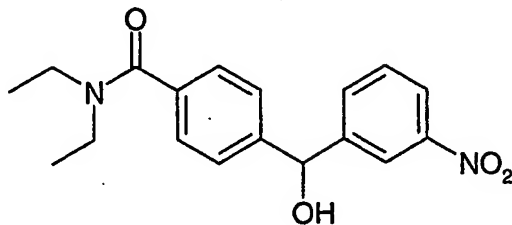
Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy
25 of pain.

Further, there is provided a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

30 In a further aspect, the present invention provides a method of preparing a compound of formula I.

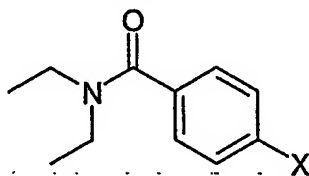
16

In one embodiment, the invention provides a process for preparing a compound of formula II, comprising:



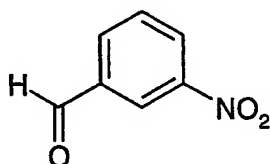
II

5 a) reacting a compound of formula III:



III

with a compound of formula IV



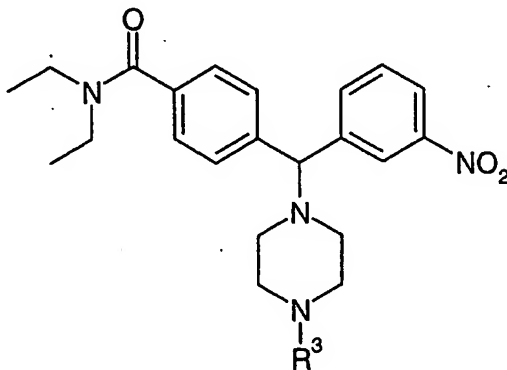
IV

10

in the presence of a base having a pKa of more than 15
wherein

X is a halogen.

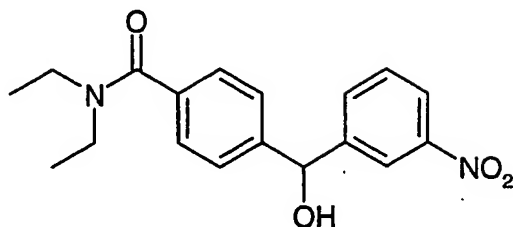
In another embodiment, the invention provides a process process for preparing
15 a compound of formula VI:



17

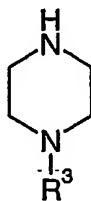
VI,

comprising: reacting a compound of formula II



II

5 with a compound of formula VII



VII

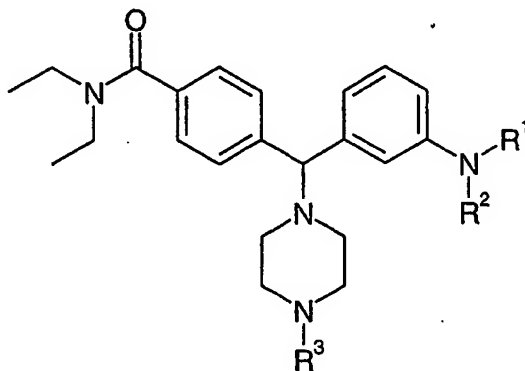
in the presence of SOX_2 to form the compound of formula VI,

wherein

10 R^3 is selected from -H, C_{1-6} alkyl-O-C(=O)-, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl- C_{1-4} alkyl, wherein said C_{1-6} alkyl-O-C(=O)-, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl- C_{1-4} alkyl are optionally substituted with one or more groups selected from C_{1-6} alkyl, halogenated C_{1-6} alkyl, $-\text{NO}_2$, $-\text{CF}_3$, C_{1-6} alkoxy and halogen; and

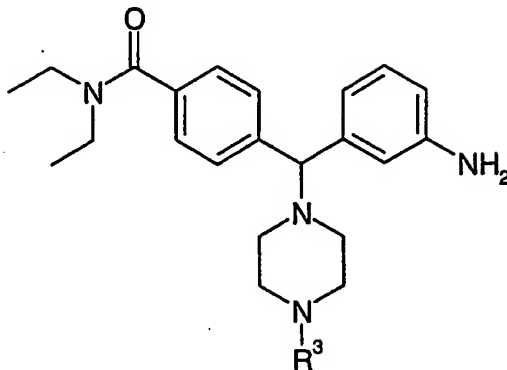
X is halogen.

15 In another embodiment, the invention provides a process for preparing a compound of formula I,



I

comprising: reacting a compound of formula VIII,



VIII

- 5 with R^9 -CHO in the presence of a reducing agent to form the compound of formula I:
wherein

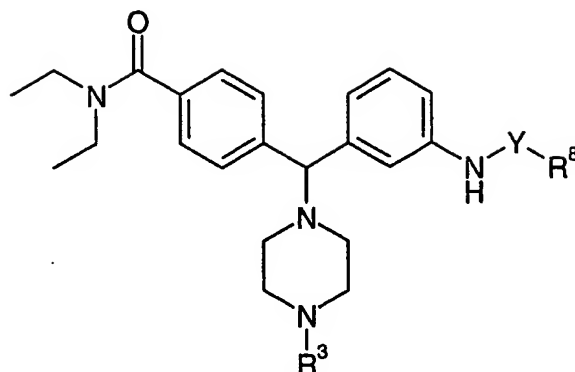
R^1 is R^9 -CH₂-, wherein R^9 is selected from phenyl, pyridyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, thiazolyl, N-oxido-pyridyl, benzyl, pyridylmethyl, thienylmethyl, furylmethyl, imidazolylmethyl, triazolylmethyl, pyrrolylmethyl, 10 thiazolylmethyl and N-oxido-pyridylmethyl, optionally substituted with one or more groups selected from C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy and halogen;

R^2 is -H; and

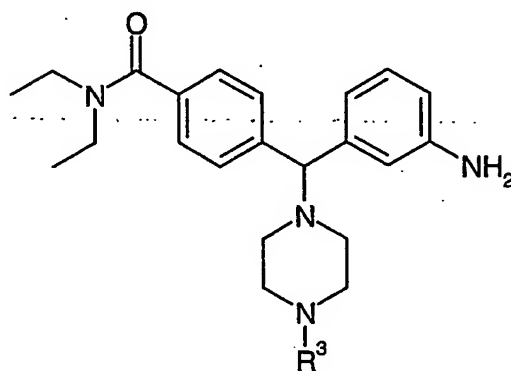
R^3 is selected from C₁₋₆alkyl-O-C(=O)-, C₁₋₆alkyl, C₃₋₆cycloalkyl, and C₃₋₆cycloalkyl-C₁₋₄alkyl, wherein said C₁₋₆alkyl-O-C(=O)-, C₁₋₆alkyl, C₃₋₆cycloalkyl, and 15 C₃₋₆cycloalkyl-C₁₋₄alkyl are optionally substituted with one or more groups selected from C₁₋₆alkyl, halogenated C₁₋₆alkyl, -NO₂, -CF₃, C₁₋₆alkoxy and halogen.

In another embodiment, the invention provides a process for preparing a compound of formula IX,

19

**IX**

comprising: reacting a compound of formula VIII,

**VIII**

5

with R^8 -Y-X or R^8 -Y-O-Y- R^8 to form the compound of formula IX:

wherein

X is halogen;

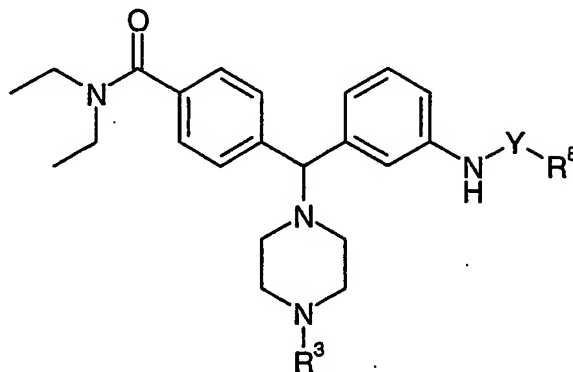
Y is selected from $-C(=O)-$ and $-S(=O)_2-$;

10 R^8 is selected from C_{3-6} alkyl, C_{6-10} aryl, C_{2-6} heteroaryl, C_{6-10} aryl- C_{1-4} alkyl, C_{2-6} heteroaryl- C_{1-4} alkyl, C_{3-10} cycloalkyl, and C_{3-10} cycloalkyl- C_{1-4} alkyl; wherein said C_{3-6} alkyl, C_{6-10} aryl, C_{2-6} heteroaryl, C_{6-10} aryl- C_{1-4} alkyl, C_{2-6} heteroaryl- C_{1-4} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl- C_{1-4} alkyl are optionally substituted with C_{1-4} alkyl, halogen, $-CF_3$, $-OH$, C_{1-3} alkoxy, phenoxy, and halogen; and

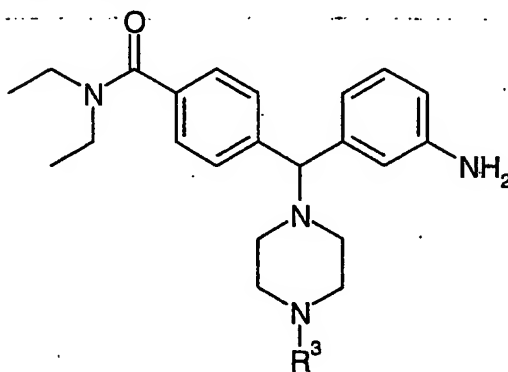
15 R^3 is selected from C_{1-6} alkyl-O-C(=O)-, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl- C_{1-4} alkyl, wherein said C_{1-6} alkyl-O-C(=O)-, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl- C_{1-4} alkyl are optionally substituted with one or more groups selected from C_{1-6} alkyl, halogenated C_{1-6} alkyl, $-NO_2$, $-CF_3$, C_{1-6} alkoxy and halogen.

20

In another embodiment, the invention provides a process for preparing a compound of formula IX,

IX

5 comprising: reacting a compound of formula VIII,



VIII

with R⁸-Z to form the compound of formula IX:

wherein

10 Z is selected from -NCO and -NCS;

Y is selected from -C(=O)NH- and -C(=S)NH-;

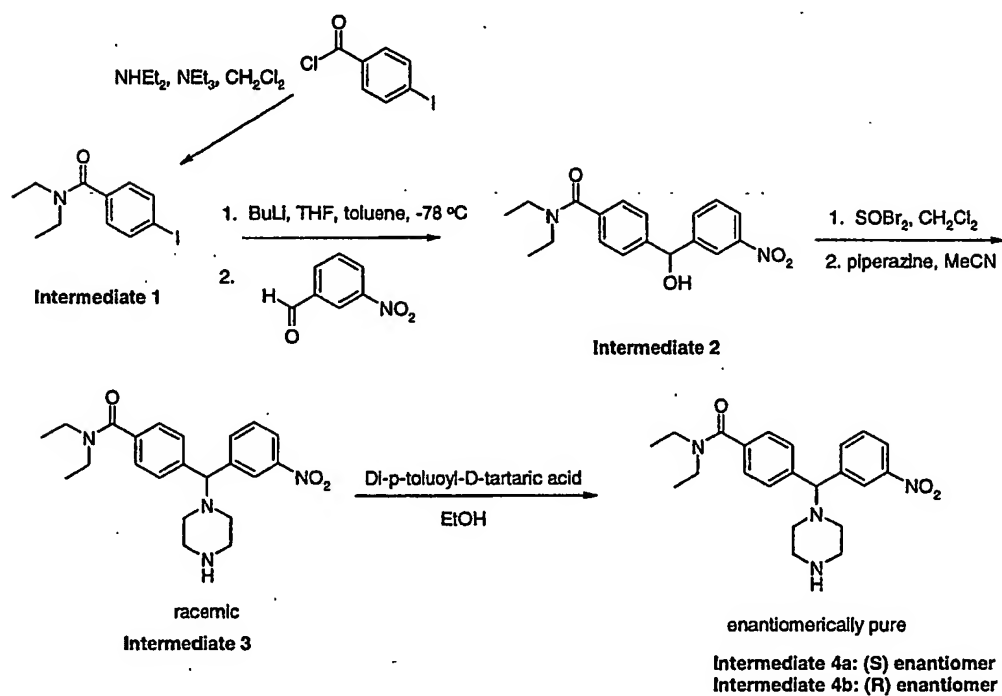
R⁸ is selected from C₃₋₆alkyl, C₆₋₁₀aryl, C₂₋₆heteroaryl, C₆₋₁₀aryl-C₁₋₄alkyl, C₂₋₆heteroaryl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl, and C₃₋₁₀cycloalkyl-C₁₋₄alkyl; wherein said C₃₋₆alkyl, C₆₋₁₀aryl, C₂₋₆heteroaryl, C₆₋₁₀aryl-C₁₋₄alkyl, C₂₋₆heteroaryl-C₁₋₄alkyl, 15 C₃₋₁₀cycloalkyl, and C₃₋₁₀cycloalkyl-C₁₋₄alkyl are optionally substituted with C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy, and halogen; and

R³ is selected from C₁₋₆alkyl-O-C(=O)-, C₁₋₆alkyl, C₃₋₆cycloalkyl, and C₃₋₆cycloalkyl-C₁₋₄alkyl, wherein said C₁₋₆alkyl-O-C(=O)-, C₁₋₆alkyl, C₃₋₆cycloalkyl,

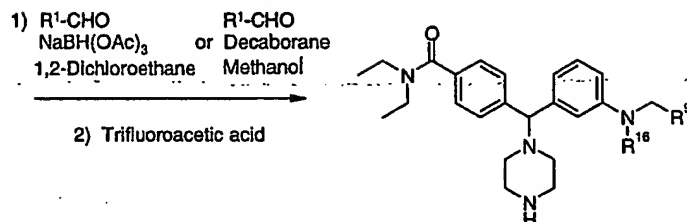
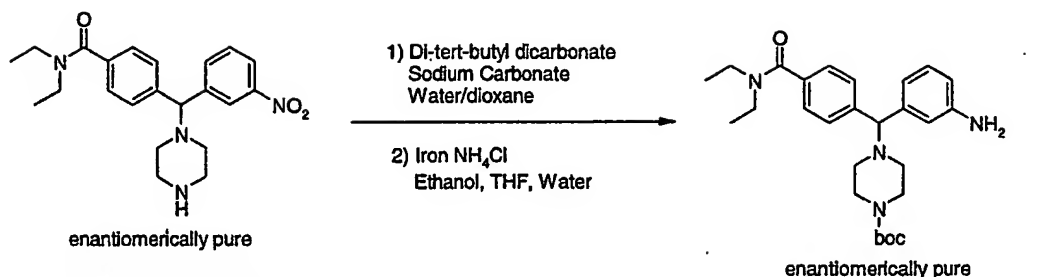
and C₃₋₆cycloalkyl-C₁₋₄alkyl are optionally substituted with one or more groups selected from C₁₋₆alkyl, halogenated C₁₋₆alkyl, -NO₂, -CF₃, C₁₋₆alkoxy and halogen.

Particularly, the compounds of the present invention can be prepared
5 according to the synthetic routes as exemplified in Schemes 1-10.

Scheme 1



Scheme 2

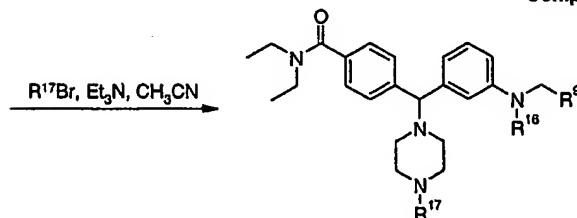


(S) enantiomers:

Compound 1: $\text{R}^9=2\text{-thiazolyl}$, $\text{R}^{16}=\text{H}$;
 Compound 3: $\text{R}^9=\text{phenyl}$, $\text{R}^{16}=\text{H}$;
 Compound 5: $\text{R}^9=2\text{-thienyl}$, $\text{R}^{16}=\text{H}$;
 Compound 6: $\text{R}^9=2\text{-furyl}$, $\text{R}^{16}=\text{H}$;
 Compound 10: $\text{R}^9=3\text{-thienyl}$, $\text{R}^{16}=\text{H}$;
 Compound 16: $\text{R}^9=\text{cyclohexyl}$, $\text{R}^{16}=\text{H}$;
 Compound 48: $\text{R}^9=\text{ethyl}$, $\text{R}^{16}=\text{H}$;
 Compound 49: $\text{R}^9=\text{ethyl}$, $\text{R}^{16}=\text{propyl}$;
 Compound 52: $\text{R}^9=4\text{-(3-pyridinyl)phenyl}$, $\text{R}^{16}=\text{H}$;
 Compound 53: $\text{R}^9=4\text{-(1H-imidazol-1-yl)phenyl}$, $\text{R}^{16}=\text{H}$;
 Compound 54: $\text{R}^9=2\text{-quinolinyl}$, $\text{R}^{16}=\text{H}$;

(R) enantiomers:

Compound 2: $\text{R}^9=3\text{-thiazolyl}$, $\text{R}^{16}=\text{H}$;
 Compound 4: $\text{R}^9=2\text{-thienyl}$, $\text{R}^{16}=\text{H}$;
 Compound 7: $\text{R}^9=\text{phenyl}$, $\text{R}^{16}=\text{H}$;
 Compound 8: $\text{R}^9=2\text{-furyl}$, $\text{R}^{16}=\text{H}$;
 Compound 9: $\text{R}^9=3\text{-thienyl}$, $\text{R}^{16}=\text{H}$;
 Compound 11: $\text{R}^9=3\text{-furyl}$, $\text{R}^{16}=\text{H}$;
 Compound 12: $\text{R}^9=\text{benzyl}$, $\text{R}^{16}=\text{H}$;
 Compound 13: $\text{R}^9=\text{cyclohexyl}$, $\text{R}^{16}=\text{H}$;
 Compound 14: $\text{R}^9=4\text{-trifluoromethyl phenyl}$, $\text{R}^{16}=\text{H}$;
 Compound 15: $\text{R}^9=\text{cyclopentyl}$, $\text{R}^{16}=\text{H}$;
 Compound 17: $\text{R}^9=\text{cyclohex-1-enyl}$, $\text{R}^{16}=\text{H}$;
 Compound 50: $\text{R}^9=\text{ethyl}$, $\text{R}^{16}=\text{H}$;
 Compound 51: $\text{R}^9=\text{ethyl}$, $\text{R}^{16}=\text{propyl}$;
 Compound 55: $\text{R}^9=1,1\text{-diphenylmethyl}$, $\text{R}^{16}=\text{H}$;
 Compound 56: $\text{R}^9=4\text{-(1,1-dimethylethyl)phenyl}$, $\text{R}^{16}=\text{H}$;
 Compound 57: $\text{R}^9=4\text{-phenoxyphenyl}$, $\text{R}^{16}=\text{H}$;

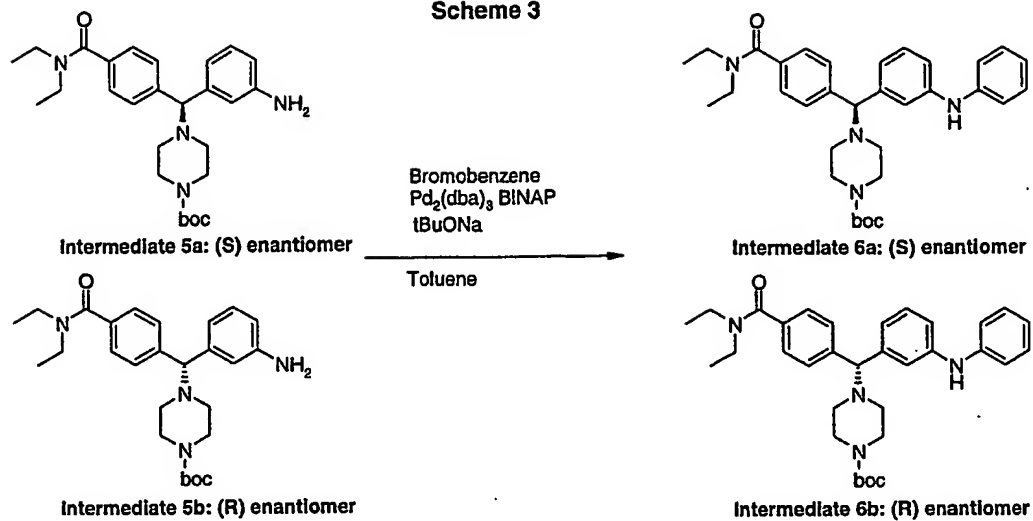


(R) enantiomer:

Compound 58: $\text{R}^9=\text{ethyl}$, $\text{R}^{16}=\text{H}$, $\text{R}^{17}=\text{allyl}$;

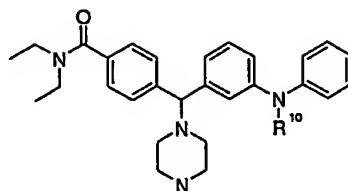
23

Scheme 3



1) Aldehyde
Decaborane
Methanol

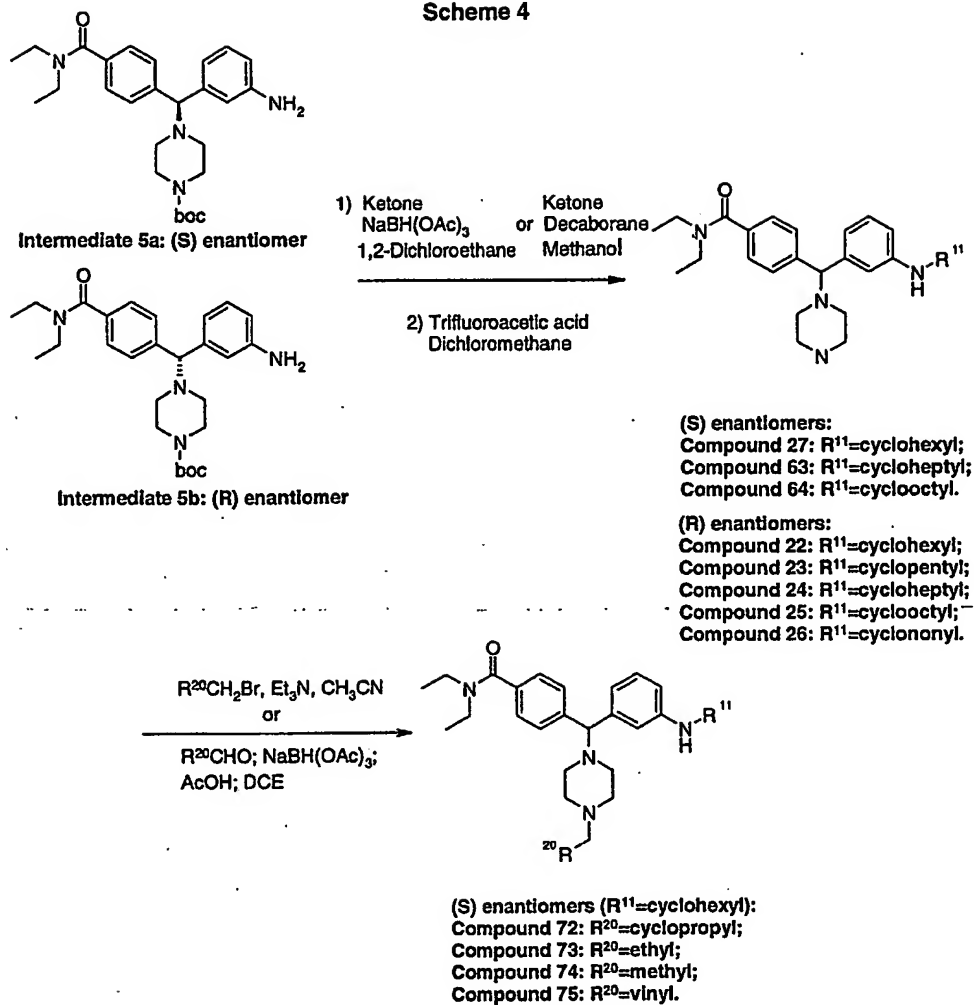
2) Trifluoroacetic acid
Dichloromethane



(S) enantiomers:
Compound 18: R^{10} =methyl;
Compound 19: R^{10} =ethyl.

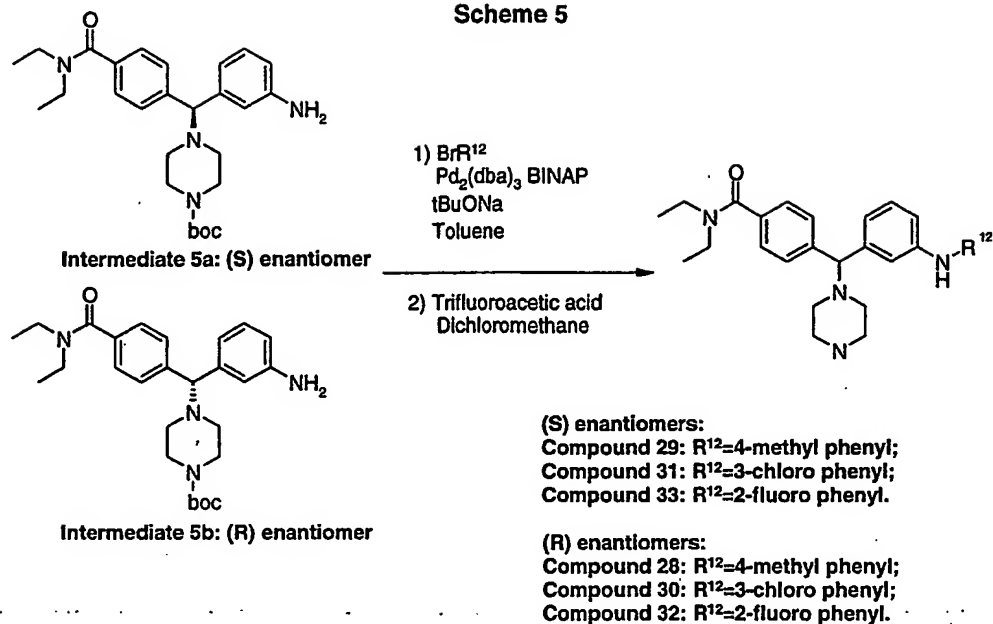
(R) enantiomers:
Compound 20: R^{10} =methyl;
Compound 21: R^{10} =ethyl.

Scheme 4

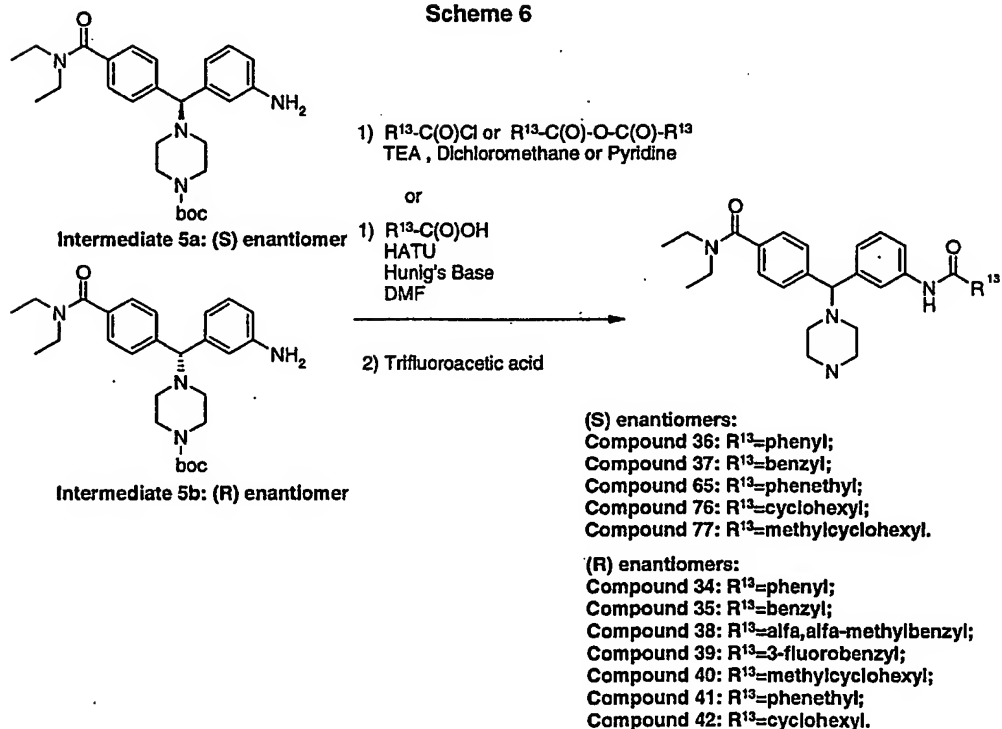


25

Scheme 5

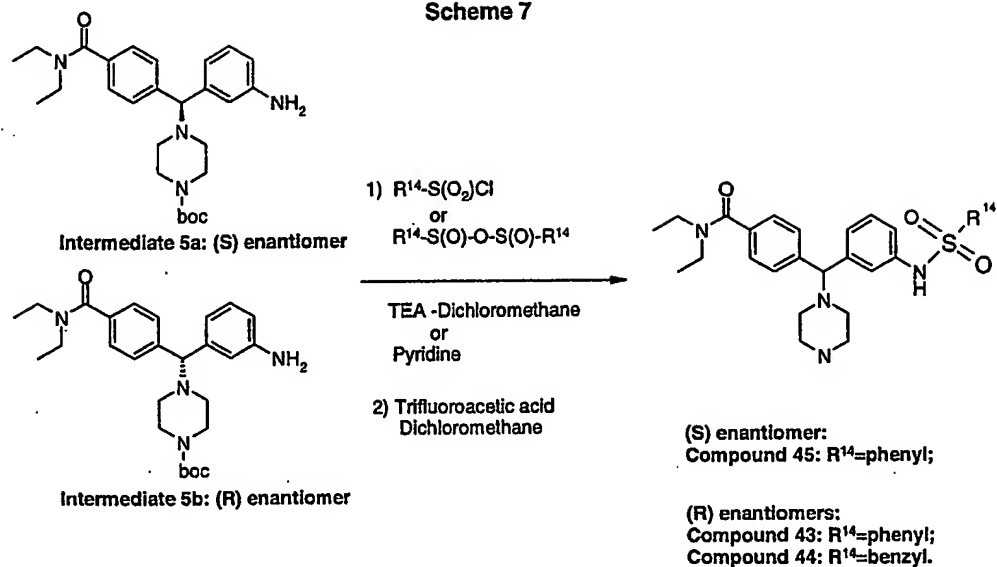


Scheme 6

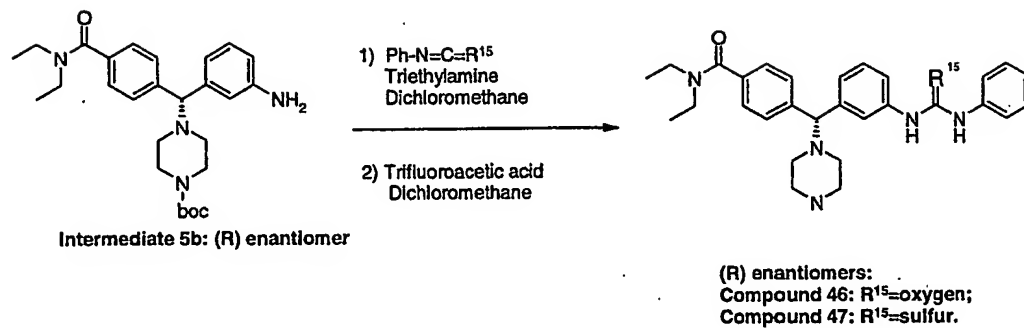


26

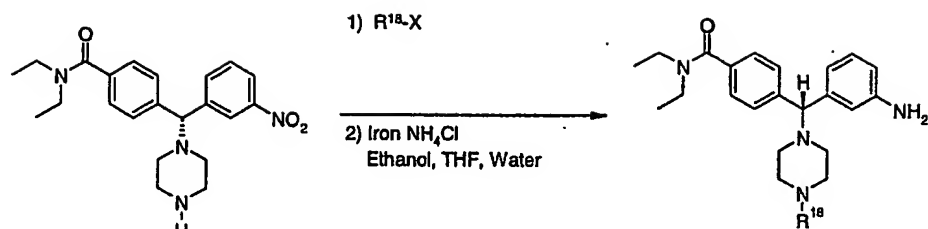
Scheme 7



Scheme 8

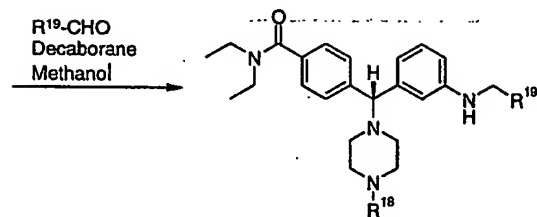


Scheme 9



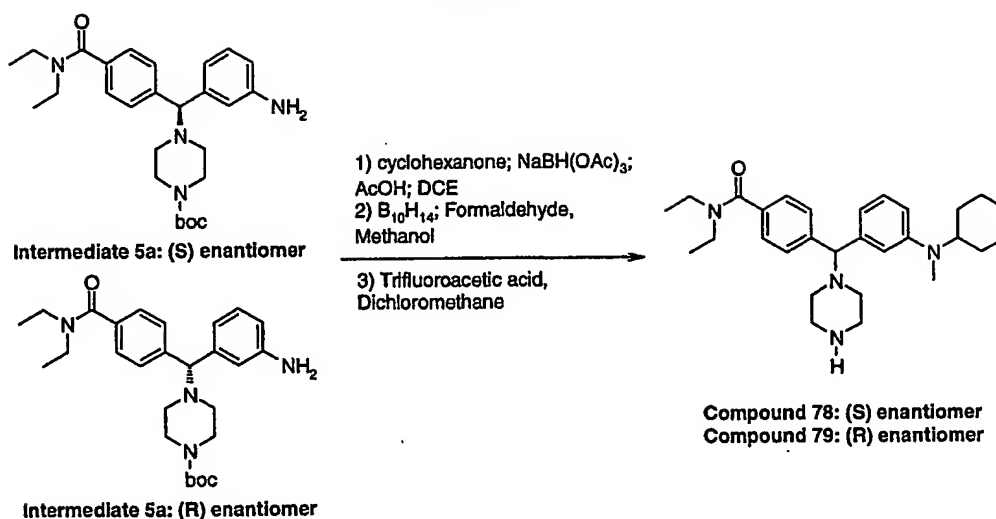
Intermediate 4b: (R) enantiomer

(R) enantiomers:
Compound 59: $R^{18}=(\text{CH}_2)_2\text{OCH}_3$;
Compound 60: $R^{18}=(\text{CH}_2)_3\text{OCH}_3$;
Compound 66: $R^{18}=\text{CH}_2\text{CHCH}_2$;
Compound 67: $R^{18}=\text{CH}_2\text{CHCMe}_2$;
Compound 68: $R^{18}=\text{CH}_2\text{cyclopropyl}$



(R) enantiomers:
Compound 61: $R^{18}=(\text{CH}_2)_2\text{OCH}_3$, $R^{19}=\text{ethyl}$;
Compound 62: $R^{18}=(\text{CH}_2)_3\text{OCH}_3$, $R^{19}=\text{ethyl}$;
Compound 69: $R^{18}=\text{CH}_2\text{CHCH}_2$, $R^{19}=2\text{-thiophene}$
Compound 70: $R^{18}=\text{CH}_2\text{CHCMe}_2$, $R^{19}=2\text{-thiophene}$
Compound 71: $R^{18}=\text{CH}_2\text{cyclopropyl}$, $R^{19}=2\text{-thiophene}$

Scheme 10



BIOLOGICAL EVALUATION

The compounds of the invention are found to be active towards δ receptors in warm-blooded animal, e.g., human. Particularly the compounds of the invention are found to be effective δ receptor ligands. *In vitro* assays, *infra*, demonstrate these surprising activities, especially with regard to agonists potency and efficacy as demonstrated in the rat brain functional assay and/or the human δ receptor functional assay (low). This feature may be related to *in vivo* activity and may not be linearly correlated with binding affinity. In these *in vitro* assays, a compound is tested for their activity toward δ receptors and IC₅₀ is obtained to determine the selective activity for a particular compound towards δ receptors. In the current context, IC₅₀ generally refers to the concentration of the compound at which 50% displacement of a standard radioactive δ receptor ligand has been observed.

The activities of the compound towards κ and μ receptors are also measured in a similar assay.

In vitro model

Cell culture

Human 293S cells expressing cloned human κ , δ and μ receptors and neomycin resistance are grown in suspension at 37°C and 5% CO₂ in shaker flasks.

containing calcium-free DMEM10% FBS, 5% BCS, 0.1% Pluronic F-68, and 600 µg/ml geneticin.

Rat brains are weighed and rinsed in ice-cold PBS (containing 2.5mM EDTA, pH 7.4). The brains are homogenized with a polytron for 30 sec (rat) in ice-cold lysis buffer (50mM Tris, pH 7.0, 2.5mM EDTA, with phenylmethylsulfonyl fluoride added just prior use to 0.5mM from a 0.5M stock in DMSO:ethanol).

Membrane preparation

Cells are pelleted and resuspended in lysis buffer (50 mM Tris, pH 7.0, 2.5 mM EDTA, with PMSF added just prior to use to 0.1 mM from a 0.1 M stock in ethanol), incubated on ice for 15 min, then homogenized with a polytron for 30 sec. The suspension is spun at 1000g (max) for 10 min at 4°C. The supernatant is saved on ice and the pellets resuspended and spun as before. The supernatants from both spins are combined and spun at 46,000 g(max) for 30 min. The pellets are resuspended in cold Tris buffer (50 mM Tris/Cl, pH 7.0) and spun again. The final pellets are resuspended in membrane buffer (50 mM Tris, 0.32 M sucrose, pH 7.0). Aliquots (1 ml) in polypropylene tubes are frozen in dry ice/ethanol and stored at -70°C until use. The protein concentrations are determined by a modified Lowry assay with sodium dodecyl sulfate.

Binding assays

Membranes are thawed at 37°C, cooled on ice, passed 3 times through a 25-gauge needle, and diluted into binding buffer (50 mM Tris, 3 mM MgCl₂, 1 mg/ml BSA (Sigma A-7888), pH 7.4, which is stored at 4°C after filtration through a 0.22 µm filter, and to which has been freshly added 5 µg/ml aprotinin, 10 µM bestatin, 10 µM diprotin A, no DTT). Aliquots of 100 µl are added to iced 12x75 mm polypropylene tubes containing 100 µl of the appropriate radioligand and 100 µl of test compound at various concentrations. Total (TB) and nonspecific (NS) binding are determined in the absence and presence of 10 µM naloxone respectively. The tubes are vortexed and incubated at 25°C for 60-75 min, after which time the contents are rapidly vacuum-filtered and washed with about 12 ml/tube iced wash buffer (50 mM Tris, pH 7.0, 3 mM MgCl₂) through GF/B filters (Whatman) presoaked for at least 2h in 0.1% polyethyleneimine. The radioactivity (dpm) retained on the filters is measured with a

beta counter after soaking the filters for at least 12h in minivials containing 6-7 ml scintillation fluid. If the assay is set up in 96-place deep well plates, the filtration is over 96-place PEI-soaked unifilters, which are washed with 3 x 1 ml wash buffer, and dried in an oven at 55°C for 2h. The filter plates are counted in a TopCount (Packard) after adding 50 µl MS-20 scintillation fluid/well.

Functional Assays

The agonist activity of the compounds is measured by determining the degree to which the compounds receptor complex activates the binding of GTP to G-proteins to which the receptors are coupled. In the GTP binding assay, GTP[γ]³⁵S is combined with test compounds and membranes from HEK-293S cells expressing the cloned human opioid receptors or from homogenised rat and mouse brain. Agonists stimulate GTP[γ]³⁵S binding in these membranes. The EC₅₀ and E_{max} values of compounds are determined from dose-response curves. Right shifts of the dose response curve by the delta antagonist naltrindole are performed to verify that agonist activity is mediated through delta receptors. For human δ receptor functional assays, EC₅₀ (low) is measured when the human δ receptors used in the assay were expressed at lower levels in comparison with those used in determining EC₅₀ (high). The E_{max} values were determined in relation to the standard δ agonist SNC80, i.e., higher than 100% is a compound that have better efficacy than SNC80.

20 Procedure for rat brain GTP

Rat brain membranes are thawed at 37°C, passed 3 times through a 25-gauge blunt-end needle and diluted in the GTPγS binding (50 mM Hepes, 20 mM NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM MgCl₂, pH 7.4, Add fresh: 1 mM DTT, 0.1% BSA). 120µM GDP final is added membranes dilutions. The EC₅₀ and E_{max} of compounds are evaluated from 10-point dose-response curves done in 300µl with the appropriate amount of membrane protein (20µg/well) and 100000-130000 dpm of GTPγ³⁵S per well (0.11 -0.14nM). The basal and maximal stimulated binding are determined in absence and presence of 3 µM SNC-80

Data analysis

The specific binding (SB) was calculated as TB-NS, and the SB in the presence of various test compounds was expressed as percentage of control SB. Values of IC_{50} and Hill coefficient (n_H) for ligands in displacing specifically bound radioligand were calculated from logit plots or curve fitting programs such as Ligand, GraphPad Prism, SigmaPlot, or ReceptorFit. Values of K_i were calculated from the Cheng-Prussoff equation. Mean \pm S.E.M. values of IC_{50} , K_i and n_H were reported for ligands tested in at least three displacement curves.

Based on the above testing protocols, we find that the compounds of the present invention and some of the intermediates used in the preparation thereof are active toward human δ receptors. Generally, the IC_{50} towards human δ receptor for most compounds of the present invention is in the range of 0.15 nM – 30.4 nM with an average of 2.30 nM. The EC_{50} and $\%E_{max}$ towards human δ receptor for these compounds are generally in the range of 2.4 nM -2325 nM and 60 – 114, respectively. The IC_{50} towards human κ and μ receptors for these compounds is generally in the ranges of 329 nM- 8457 nM and 16 nM – 9560 nM, respectively.

Receptor Saturation Experiments

Radioligand K_d values are determined by performing the binding assays on cell membranes with the appropriate radioligands at concentrations ranging from 0.2 to 5 times the estimated K_d (up to 10 times if amounts of radioligand required are feasible). The specific radioligand binding is expressed as pmole/mg membrane protein. Values of K_d and B_{max} from individual experiments are obtained from nonlinear fits of specifically bound (B) vs. nM free (F) radioligand from individual according to a one-site model.

Determination Of Mechano-Allodynia Using Von Frey Testing

Testing is performed between 08:00 and 16:00h using the method described by Chaplan et al. (1994). Rats are placed in Plexiglas cages on top of a wire mesh bottom which allows access to the paw, and are left to habituate for 10-15 min. The area tested is the mid-plantar left hind paw, avoiding the less sensitive foot pads. The paw is touched with a series of 8 Von Frey hairs with logarithmically incremental

stiffness (0.41, 0.69, 1.20, 2.04, 3.63, 5.50, 8.51, and 15.14 grams; Stoelting, Ill, USA). The von Frey hair is applied from underneath the mesh floor perpendicular to the plantar surface with sufficient force to cause a slight buckling against the paw, and held for approximately 6-8 seconds. A positive response is noted if the paw is sharply withdrawn. Flinching immediately upon removal of the hair is also considered a positive response. Ambulation is considered an ambiguous response, and in such cases the stimulus is repeated.

Testing Protocol

The animals are tested on postoperative day 1 for the FCA-treated group. The 50% withdrawal threshold is determined using the up-down method of Dixon (1980). Testing is started with the 2.04 g hair, in the middle of the series. Stimuli are always presented in a consecutive way, whether ascending or descending. In the absence of a paw withdrawal response to the initially selected hair, a stronger stimulus is presented; in the event of paw withdrawal, the next weaker stimulus is chosen. Optimal threshold calculation by this method requires 6 responses in the immediate vicinity of the 50% threshold, and counting of these 6 responses begins when the first change in response occurs, e.g. the threshold is first crossed. In cases where thresholds fall outside the range of stimuli, values of 15.14 (normal sensitivity) or 0.41 (maximally allodynic) are respectively assigned. The resulting pattern of positive and negative responses is tabulated using the convention, X = no withdrawal; O = withdrawal, and the 50% withdrawal threshold is interpolated using the formula:

$$50\% \text{ g threshold} = 10^{(X_f + k\delta)} / 10,000$$

where X_f = value of the last von Frey hair used (log units); k = tabular value (from Chaplan et al. (1994)) for the pattern of positive / negative responses; and δ = mean difference between stimuli (log units). Here $\delta = 0.224$.

Von Frey thresholds are converted to percent of maximum possible effect (% MPE), according to Chaplan et al. 1994. The following equation is used to compute % MPE:

$$\% \text{ MPE} = \frac{\text{Drug treated threshold (g)} - \text{allodynia threshold (g)}}{\text{Control threshold (g)} - \text{allodynia threshold (g)}} \times 100$$

Administration Of Test Substance

Rats are injected (subcutaneously, intraperitoneally, intravenously or orally) with a test substance prior to von Frey testing, the time between administration of test compound and the von Frey test varies depending upon the nature of the test compound.

Writhing Test

Acetic acid will bring abdominal contractions when administered intraperitoneally in mice. These will then extend their body in a typical pattern. When analgesic drugs are administered, this described movement is less frequently observed and the drug selected as a potential good candidate.

A complete and typical Writhing reflex is considered only when the following elements are present: the animal is not in movement; the lower back is slightly depressed; the plantar aspect of *both* paws is observable. In this assay, compounds of the present invention demonstrate significant inhibition of writhing responses after oral dosing of 1-100 $\mu\text{mol/kg}$.

(i) Solutions preparation

Acetic acid (AcOH): 120 μL of Acetic Acid is added to 19.88 ml of distilled water in order to obtain a final volume of 20 ml with a final concentration of 0.6% AcOH. The solution is then mixed (vortex) and ready for injection.

Compound (drug): Each compound is prepared and dissolved in the most suitable vehicle according to standard procedures.

(ii) Solutions administration

The compound (drug) is administered orally, intraperitoneally (i.p.), subcutaneously (s.c.) or intravenously (i.v.) at 10 ml/kg (considering the average mice body weight) 20, 30 or 40 minutes (according to the class of compound and its characteristics) prior to testing. When the compound is delivered centrally: Intraventricularly (i.c.v.) or intrathecally (i.t.) a volume of 5 μL is administered.

The AcOH is administered intraperitoneally (i.p.) in two sites at 10 ml/kg (considering the average mice body weight) immediately prior to testing.

(iii) Testing

The animal (mouse) is observed for a period of 20 minutes and the number of occasions (Writhing reflex) noted and compiled at the end of the experiment. Mice are
5 kept in individual "shoe box" cages with contact bedding. A total of 4 mice are usually observed at the same time: one control and three doses of drug.

For the anxiety and anxiety-like indications, efficacy has been established in the geller-seifter conflict test in the rat.

For the functional gastrointestinal disorder indication, efficacy can be
10 established in the assay described by Coutinho SV *et al*, in American Journal of Physiology - Gastrointestinal & Liver Physiology. 282(2):G307-16, 2002 Feb, in the rat.

ADDITIONAL IN VIVO TESTING PROTOCOLS

Subjects and housing

15 Naïve male Sprague Dawley rats (175-200g) are housed in groups of 5 in a temperature controlled room (22°C, 40-70% humidity, 12-h light/dark). Experiments are performed during the light phase of the cycle. Animals have food and water ad libitum and are sacrificed immediately after data acquisition.

Sample

20 Compound (Drug) testing includes groups of rats that do not receive any treatment and others that are treated with E. coli lipopolysaccharide(LPS). For the LPS-treated experiment, four groups are injected with LPS, one of the four groups is then vehicle-treated whilst the other three groups are injected with the drug and its vehicle. A second set of experiments are conducted involving five groups of rats; all
25 of which receive no LPS treatment. The naïve group receives no compound (drug) or vehicle; the other four groups are treated with vehicle with or without drug. These are performed to determine anxiolytic or sedative effects of drugs which can contribute to a reduction in USV.

Administration of LPS

Rats are allowed to habituate in the experimental laboratory for 15-20 min prior to treatment. Inflammation is induced by administration of LPS (endotoxin of gram-negative *E. coli* bacteria serotype 0111:B4, Sigma). LPS (2.4µg) is injected
5 intracerebro-ventricularly (i.c.v.), in a volume of 10µl, using standard stereotaxic surgical techniques under isoflurane anaesthesia. The skin between the ears is pushed rostrally and a longitudinal incision of about 1cm is made to expose the skull surface. The puncture site is determined by the coordinates: 0.8 mm posterior to the bregma, 1.5 mm lateral (left) to the lambda (sagittal suture), and 5 mm below the surface of the
10 skull (vertical) in the lateral ventricle. LPS is injected via a sterile stainless steel needle (26-G 3/8) of 5 mm long attached to a 100-µl Hamilton syringe by polyethylene tubing (PE20; 10-15 cm). A 4 mm stopper made from a cut needle (20-G) is placed over and secured to the 26-G needle by silicone glue to create the desired 5mm depth.

15 Following the injection of LPS, the needle remains in place for an additional 10 s to allow diffusion of the compound, then is removed. The incision is closed, and the rat is returned to its original cage and allowed to rest for a minimum of 3.5h prior to testing.

Experimental setup for air-puff stimulation

20 The rats remains in the experimental laboratory following LPS injection and compound (drug) administration. At the time of testing all rats are removed and placed outside the laboratory. One rat at a time is brought into the testing laboratory and placed in a clear box (9 × 9 × 18 cm) which is then placed in a sound-attenuating ventilated cubicle measuring 62(w) × 35(d) × 46(h) cm (BRS/LVE, Div. Tech-Serv
25 Inc). The delivery of air-puffs, through an air output nozzle of 0.32 cm, is controlled by a system (AirStim, San Diego Instruments) capable of delivering puffs of air of fixed duration (0.2 s) and fixed intensity with a frequency of 1 puff per 10s. A maximum of 10 puffs are administered, or until vocalisation starts, whichever comes first. The first air puff marks the start of recording.

Experimental setup for and ultrasound recording

The vocalisations are recorded for 10 minutes using microphones (G.R.A.S. sound and vibrations, Vedbaek, Denmark) placed inside each cubicle and controlled by LMS (LMS CADA-X 3.5B, Data Acquisition Monitor, Troy, Michigan) software.

- 5 The frequencies between 0 and 32000Hz are recorded, saved and analysed by the same software (LMS CADA-X 3.5B, Time Data Processing Monitor and UPA (User Programming and Analysis)).

Compounds (Drugs)

- 10 All compounds (drugs) are pH-adjusted between 6.5 and 7.5 and administered at a volume of 4 ml/kg. Following compound (drug) administration, animals are returned to their original cages until time of testing.

Analysis

- 15 The recording is run through a series of statistical and Fourier analyses to filter (between 20-24kHz) and to calculate the parameters of interest. The data are expressed as the mean \pm SEM. Statistical significance is assessed using T-test for comparison between naive and LPS-treated rats, and one way ANOVA followed by Dunnett's multiple comparison test (post-hoc) for drug effectiveness. A difference between groups is considered significant with a minimum p value of ≤ 0.05 . Experiments are repeated a minimum of two times.

20

EXAMPLES

- The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed
25 as limiting the invention.

INTERMEDIATE 1: 4-Iodo-N,N-diethylbenzamide

- To a mixture of 4-iodo-benzoyl chloride (75 g) in 500 mL CH_2Cl_2 was added a mixture of Et_3N (50 mL) and Et_2NH (100 mL) at 0 $^\circ\text{C}$. After the addition, the
30 resulting reaction mixture was warmed up to room temperature in 1 hr and was then

washed with saturated ammonium chloride. The organic extract was dried (Na_2SO_4), filtered and concentrated. Residue was recrystallized from hot hexanes to give 80 g of INTERMEDIATE 1.

- 5 **INTERMEDIATE 2: 4-[hydroxy(3-nitrophenyl)methyl]-*N,N*-diethylbenzamide**
N,N-Diethyl-4-iodobenzamide (5.0 g, 16 mmol) was dissolved in THF (150 mL) and cooled to -78°C under nitrogen atmosphere. *n*-BuLi (15 mL, 1.07 M solution in hexane, 16 mmol) was added dropwise during 10 min at -65 to -78°C . The solution was then cannulated into 3-nitrobenzaldehyde (2.4 g, 16 mmol) in toluene/THF
10 (approx. 1:1, 100 mL) at -78°C . NH_4Cl (aq.) was added after 30 min. After concentration *in vacuo*, extraction with EtOAc / water, drying (MgSO_4) and evaporation of the organic phase, the residue was purified by chromatography on silica (0 – 75% EtOAc/heptane) to give INTERMEDIATE 2 (2.6 g, 50%). ^1H NMR (CDCl_3) δ 1.0-1.3 (m, 6H), 3.2, 3.5 (2m, 4H), 5.90 (s, 1H), 7.30-7.40 (m, 4H), 7.50
15 (m, 1H), 7.70 (d, $J = 8\text{Hz}$, 1H), 8.12 (m, 1H), 8.28 (m, 1H).

INTERMEDIATE 3: *N,N*-diethyl-4-[(3-nitrophenyl)(1-piperazinyl)methyl]benzamide

- To a solution of alcohol INTERMEDIATE 2 (10.01g, 30.5 mmol) in dichloromethane
20 (200 mL) was added thionyl bromide (2.58 mL, 33.6 mmol). After one hour at room temperature the reaction was washed with saturated aqueous sodium bicarbonate (100 mL) and the organic layer was separated. The aqueous layer was washed with dichloromethane (3 x 100 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated.
- 25 The crude benzyl bromide was dissolved in acetonitrile (350 mL) and piperazine (10.5g, 122 mmol) was added. After heating the reaction for one hour at 65°C the reaction was washed with saturated ammonium chloride/ethyl acetate and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x 100 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated to
30 give racemic INTERMEDIATE 3.

INTERMEDIATE 4a: Enantiomerically Pure *N,N*-diethyl-4-[(S)-(3-nitrophenyl)(1-piperazinyl)methyl]benzamide and 4b: Enantiomerically Pure *N,N*-diethyl-4-[(R)-(3-nitrophenyl)(1-piperazinyl)methyl]benzamide

Racemic INTERMEDIATE 3 is resolved to give enantiomerically pure

5 INTERMEDIATE 4a and 4b as follows:

The INTERMEDIATE 3 was dissolved in ethanol (150 mL) and di-*p*-toluoyl-D-tartaric acid (11.79 g, 1 equivalent) was added. The product precipitated out over a 12 hour period. The solid was collected by filtration and was redissolved in refluxing ethanol until all of the solid dissolved (approximately 1200 mL ethanol). Upon

10 cooling the solid was collected by filtration and the recrystallation repeated a second time. The solid was collected by filtration and was treated with aqueous sodium hydroxide (2 M) and was extracted with ethyl acetate. The organic extract was then dried (Na₂SO₄), filtered and concentrated to give 1.986 g of enantiomerically pure INTERMEDIATE 4b. This INTERMEDIATE 4b has a negative optical rotation ¹H
15 NMR (400MHz, CDCl₃) δ 1.11 (br s, 3H), 1.25 (br s, 3H), 2.37 (br s, 4H), 2.91 (t, J = 5Hz, 4H), 3.23 (br s, 2H), 3.52 (br s, 2H), 4.38 (s, 1H), 7.31-7.33 (m, 2H), 7.41-7.43 (m, 2H), 7.47 (t, J = 8Hz, 1H), 7.75-7.79 (m, 1H), 8.06-8.09 (m, 1H), 8.30-8.32 (m, 1H).

20 **INTERMEDIATE 4b: Enantiomerically Pure *N,N*-diethyl-4-[(S)-(3-nitrophenyl)(1-piperazinyl)methyl]benzamide and 4b**

The (S) enantiomer INTERMEDIATE 4a may be obtained by performing the above resolution procedure with di-*p*-toluoyl-L-tartaric acid.

Chiral purity was determined by HPLC using the following conditions:

25 Chiralpack AD column (Daicel Chemical Industries);
Flow rate 1 mL/minute;
Run time 30 minutes at 25 °C;
Isocratic 15% ethanol 85% hexanes.

30 **INTERMEDIATE 5a or 5b: tert -Butyl 4-((3-aminophenyl){4-((diethylamino)carbonyl)phenyl)methyl}piperazine-1-carboxylate**

To a solution of INTERMEDIATE 4a or 4b (300 mg) in dioxane (40 mL) was added di-*tert*-butyl dicarbonate (247 g; 1.5 eq). Sodium carbonate (119 g; 1.5 eq) was dissolved in water (15 mL) and then added in the dioxane solution. After 12 hours the solution was concentrated and saturated sodium bicarbonate was then added. The aqueous solution was extracted with three portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated to afford a white foam. Without further purification, the foam was then dissolved in a mixture of ethanol, tetrahydrofuran, water and saturated ammonium chloride (15 mL; ratios 4:2:1:1 v/v). Iron granules (422 g; 10 eq) were added and the solution was heated at 90 °C for 1.5 hour. The resulting mixture was cooled, filtered through celite and concentrated. Saturated sodium bicarbonate was added and the aqueous solution was extracted with three portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated to afford a white foam INTERMEDIATE 5a or 5b, respectively. The product can be use without any further purification. (92-99 % yield),
¹H NMR (400MHz, CDCl₃) 1.06-1.16 (m, 3H), 1.17-1.26 (m, 3H), 1.44 (s, 9H), 2.28-2.39 (m, 4H), 3.20-3.31 (br s, 2H), 3.37-3.44 (br s, 2H), 3.48-3.58 (br s, 2H), 3.60-3.70 (br s, 2H), 4.12 (s, 1H), 6.51-6.55 (m, 1H), 6.72 (t, J = 2.13Hz, 1H), 6.79 (d, J = 8.17Hz, 1H), 7.06 (t, J = 7.46Hz, 1H), 7.29 (d, J = 7.82Hz, 2H), 7.43 (d, J = 7.82Hz, 2H).

INTERMEDIATE 6a *tert*-butyl 4-((*R*)-(3-anilinophenyl){4-[(diethylamino)carbonyl]phenyl)methyl}piperazine-1-carboxylate or 6b *tert*-butyl 4-((*R*)-(3-anilinophenyl){4-

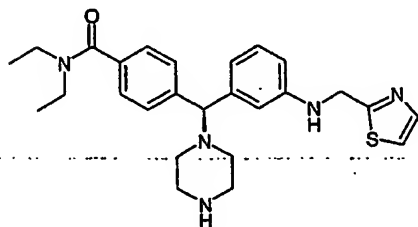
[(diethylamino)carbonyl]phenyl)methyl}piperazine-1-carboxylate

To a solution of INTERMEDIATE 5a or 5b (325 mg) in toluene (2 mL) was added bromo benzene (94 µL; 1.3 eq), Pd₂(dba)₃ (25 g; 0.04 eq), Sodium *tert*-butoxide (93 g; 1.4 eq) and BINAP (34 g; 0.08 eq). The solution was heated in the microwave in a sealed tube for 5 min at 110°C. The resulting mixture filtered through celite and concentrated. The crude was purified by a normal phase MPLC with a disposable silica gel column (40 g); eluting 40% to 60% ethyl acetate in hexane. Pure fraction was collected and concentrated to afford yellow foam (338 g; 89% yield).

40

¹H NMR (400MHz, CDCl₃) 1.07 (t, J = 6.64Hz, 3H), 1.19 (t, J = 6.83Hz, 3H), 1.40 (s, 9H), 2.28-2.39 (m, 4H), 3.20-3.31 (br s, 2H), 3.20-3.27 (m, 2H), 3.37-3.43 (m, 4H), 3.45-3.53 (m, 2H), 4.21 (s, 1H), 6.80 (tt, J = 7.35, 1.15Hz, 1H), 6.84-6.88 (m, 2H), 6.95-6.99 (m, 2H), 7.09 (t, J = 8.00Hz, 1H), 7.13-7.19 (m, 3H), 7.28 (d, J = 8.40Hz, 2H), 7.51 (d, J = 8.20Hz, 2H).

COMPOUND 1: N,N-diethyl-4-((S)piperazin-1-yl{3-[(1,3-thiazol-2-ylmethyl)amino]phenyl)methyl)benzamide

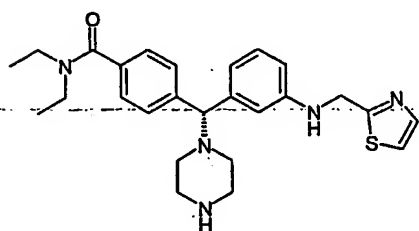


10

To a solution of INTERMEDIATE 5a (477 mg) in 1,2-dichloroethane (15 mL) was added 2-thiazole carboxaldehyde (179 μ L; 2 eq) and sodium triacetoxyborohydride (432 g; 2 eq). The reaction was stirred at room temperature under nitrogen. After 24 hours the reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was dissolved in dichloromethane (15 mL) and trifluoroacetic acid (1.5 mL) was added. The reaction was allowed to stir overnight. The solution was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography eluting with 5% methanol, 1% ammonium hydroxide in dichloromethane rising to 15% methanol, 1.5% ammonium hydroxide in dichloromethane. The product obtained was further purified by reverse phase chromatography, eluting 5% to 55% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 1 (162 mg, 20%

yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.07 (br s, 1H), 1.2 (br s, 1H), 2.55 (br s, 4H), 3.09-3.31 (m, 6H), 3.49 (br s, 2H), 4.26 (s, 1H), 4.61 (s, 2H), 6.5 (d, J = 8.51Hz, 1H), 6.69 (s, 2H), 7.01 (t, J = 7.57Hz, 1H), 7.22-7.28 (m, 2H), 7.40-7.47 (m, 3H), 7.73 (s, 1H). Found: C, 53.09; H, 5.52; N, 10.07. C₂₆H₃₃N₅OS x 1.6CF₃CO₂H x 0.8H₂O has C, 53.10 H, 5.52; N, 10.60 %.

COMPOUND 2: N,N-diethyl-4-((R)-piperazin-1-yl{3-[(1,3-thiazol-2-ylmethyl)amino]phenyl)methyl)benzamide

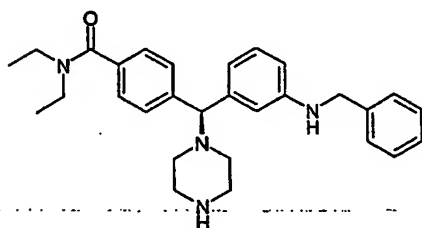


To a solution of INTERMEDIATE 5b (167 mg) in 1,2-dichloroethane (10 mL) was added 2-thiazole carboxaldehyde (62 µL; 2 eq) and sodium triacetoxyborohydride (152 g; 2 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours the reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was dissolved in dichloromethane (10 mL) and trifluoroacetic acid (1 mL) was added. After 18 hours the solution was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 5% to 50% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 2 (90 mg, 31% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.07 (br s, 1H), 1.2 (br s, 1H), 2.55 (br s, 4H),

3.09-3.31 (m, 6H), 3.49 (br s, 2H), 4.26 (s, 1H), 4.61 (s, 2H), 6.5 (d, $J = 8.51\text{Hz}$, 1H), 6.69 (s, 2H), 7.01 (t, $J = 7.57\text{Hz}$, 1H), 7.22-7.28 (m, 2H), 7.40-7.47 (m, 3H), 7.73 (s, 1H). Found: C, 48.90; H, 5.12 N, 9.13. $\text{C}_{26}\text{H}_{33}\text{N}_5\text{OS} \times 2.4\text{CF}_3\text{CO}_2\text{H} \times 1.1\text{H}_2\text{O}$ has C, 48.86 H, 5.01; N, 9.25%. $[\alpha]_{\text{D}} = -23.68\text{ deg}$ [c 0.625, MeOH].

5

COMPOUND 3: 4-[(S)-[3-(benzylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide



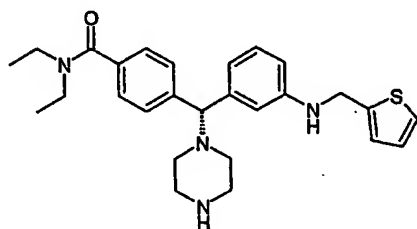
10

To a solution of INTERMEDIATE 5a (176 mg) in 1,2-dichloroethane (10 mL) was added benzaldehyde (77 μL ; 2eq) and sodium triacetoxyborohydride (159 g; 2 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours the reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was dissolved in dichloromethane (10 mL) and trifluoroacetic acid (1 mL) was added. After 18 hours the solution was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 5% to 50% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 3 (127 mg, 42% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.07 (m, 3H), 1.20 (m, 3H), 2.53 (br s, 4H), 3.13 (q, $J = 5.1\text{Hz}$, 4H), 3.20-3.25 (m, 2H), 3.45-3.51 (m, 2H), 4.31 (s, 1H), 4.38, (s, 2H), 6.73-6.78 (m, 1H), 6.85-6.93 (m, 2H), 7.14 (t, $J = 7.6\text{Hz}$, 1H), 7.23-7.33 (m, 7H), 7.43

25

(d, J = 8.0Hz, 2H). Found: C, 53.88; H, 5.25; N, 7.40. $C_{29}H_{36}N_4O \times 2.6CF_3CO_2H \times 0.5H_2O$ has C, 53.90; H, 5.24; N, 7.35 %. $[\alpha]_D^{20} = +25.74$ deg [c0.672, MeOH].

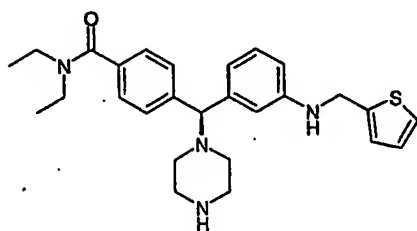
COMPOUND 4: N,N-diethyl-4-((R)-piperazin-1-yl{3-[(thien-2-ylmethyl)amino]phenyl)methyl)benzamide



To a solution of INTERMEDIATE 5b (158 mg) in 1,2-dichloroethane (10 mL) was
10 added 2-thiophene carboxaldehyde (63 μ L; 2 eq) and sodium triacetoxyborohydride (144 g; 2 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours the reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium
15 sulfate, filtered and concentrated. The residue was dissolved in dichloromethane (10 mL) and trifluoroacetic acid (1 mL) was added. After 18 hours the solution was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The
20 residue was purified by reverse phase chromatography, eluting 5% to 50% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 4 (62 mg, 12% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; 1H NMR (400MHz CD_3OD) 1.07 (m, 3H), 1.20 (m, 3H), 2.51-2.61 (m, 4H),
25 3.13-3.18 (m, 4H), 3.19-3.25 (m, 2H), 3.45-3.52 (m, 2H), 4.30 (s, 1H), 4.50 (s, 2H), 6.62 (ddd, J = 8.14, 2.26, 0.94Hz, 1H), 6.76 (d, J = 7.59Hz, 1H), 6.82 (t, J = 2.16Hz, 1H), 6.92 (dd, J = 5.03, 3.45Hz, 1H), 6.95-6.98 (m, 1H), 7.06 (t, J = 7.91Hz, 1H), 7.23 (dd, J = 5.03, 1.15Hz, 1H), 7.27 (d, J = 8.34Hz, 2H), 7.47 (d, J = 8.20Hz, 2H). Found:

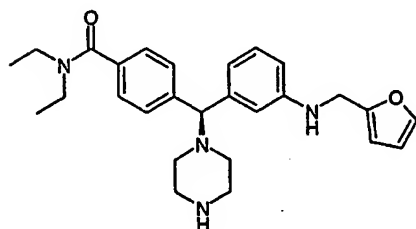
C, 53.07; H, 5.26; N, 8.22. $C_{27}H_{34}N_4OS \times 2.0CF_3CO_2H \times 0.6H_2O$ has C, 53.08; H, 5.35 N, 7.39 %. $[\alpha]_D^{20} = -27.71 \text{ deg } [c0.635, \text{MeOH}]$.

COMPOUND 5: N,N-diethyl-4-((S)-piperazin-1-yl{3-[(thien-2-ylmethyl)amino]phenyl)methyl)benzamide



To a solution INTERMEDIATE 5a (150 mg) in 1,2-dichloroethane (10 mL) was
 10 added 2-thiophenecarboxaldehyde (33 μ L; 1.1 eq) and sodium triacetoxyborohydride (74 g; 1.1 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, trifluoroacetic acid (1 mL) was added to the reaction and stirred for 4 hours until complete removal of the boc group. The reaction was diluted with
 15 dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography with a gradient from 5% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was
 20 obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 5 (118 mg, 46% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; 1H NMR (400MHz, CD_3OD) 1.07 (m, 3H), 1.20 (m, 3H), 2.51-2.61 (m, 4H), 3.13-3.18 (m, 4H), 3.19-3.25 (m, 2H), 3.45-3.52 (m, 2H), 4.30 (s, 1H), 4.50 (s, 2H), 6.62 (ddd, $J = 8.14, 2.26, 0.94\text{Hz}$, 1H), 6.76 (d, $J = 7.59\text{Hz}$, 1H), 6.82 (t, $J = 2.16\text{Hz}$, 1H), 6.92 (dd, $J = 5.03, 3.45\text{Hz}$, 1H), 6.95-6.98 (m, 1H), 7.06 (t, $J = 7.91\text{Hz}$, 1H), 7.23 (dd, $J = 5.03, 1.15\text{Hz}$, 1H), 7.27 (d, $J = 8.34\text{Hz}$, 2H), 7.47 (d, $J = 8.20\text{Hz}$, 2H). Found: C, 48.42; H, 4.70; N, 6.91. $C_{27}H_{34}N_4OS \times 3.0CF_3CO_2H \times 0.8H_2O$ has C, 48.39 H, 4.75; N, 6.84 %. $[\alpha]_D = +21.30\text{deg } [c 0.784, \text{MeOH}]$.

COMPOUND 6: N,N-diethyl-4-[(S)-{3-[(2-furylmethyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide



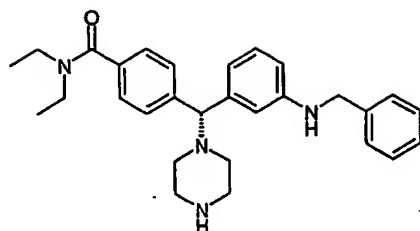
5

To a solution of INTERMEDIATE 5a (150 mg) in 1,2-dichloroethane (10 mL) was added 2-furaldehyde (29 μ L; 1.1 eq) and sodium triacetoxyborohydride (74 g; 1.1 eq).

The reaction was stirred at room temperature under nitrogen. After 18 hours, trifluoroacetic acid (1 mL) was added to the reaction and stirred for 4 hours until

- 10 complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 5% to 45% acetonitrile in water containing
- 15 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 6 (82 mg, 33% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.09 (t, J = 6.80Hz, 3H), 1.21 (t, J = 6.7Hz, 3H), 2.58-2.65 (m, 4H), 3.19-3.26 (m, 6H), 3.51 (q, J = 7.50Hz, 2H), 4.38 (s, 2H), 4.39 (s, 1H), 6.23 (d, J = 2.93Hz,
- 20 1H), 6.31-6.34 (m, 1H), 6.75-6.79 (m, 1H), 6.96 (d, J = 7.42Hz, 2H), 7.17 (t, J = 7.60Hz, 1H), 7.31 (d, J = 8.20Hz, 2H), 7.44 (s, 1H), 7.52 (d, J = 8.20Hz, 2H). Found: C, 51.70; H, 5.20; N, 7.53. $\text{C}_{27}\text{H}_{34}\text{N}_4\text{O}_2 \times 2.5\text{CF}_3\text{CO}_2\text{H} \times 0.6\text{H}_2\text{O} \times 0.1\text{CH}_3\text{OH}$ has C, 51.71; H, 5.15; N, 7.51 %. $[\alpha]_{\text{D}} = +14.72^\circ$ [c 0.679, MeOH].

- 25 **COMPOUND 7: 4-[(R)-[3-(benzylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide**

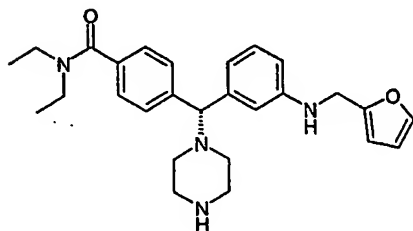


To a solution of INTERMEDIATE 5b (90 mg) in 1,2-dichloroethane (5 mL) was added benzaldehyde (21 μ L; 1.1 eq) and sodium triacetoxyborohydride (45 g; 1.1eq).

- 5 The reaction was stirred at room temperature under nitrogen. After 18 hours, trifluoroacetic acid (1 mL) was added to the reaction and stirred for 4 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over
- 10 anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 7 (48 mg, 31% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.07 (m, 3H), 1.20 (m, 3H), 2.53 (br s, 4H), 3.13 (q, $J = 5.1\text{Hz}$, 4H), 3.20-3.25 (m, 2H), 3.45-3.51 (m, 2H), 4.31 (s, 1H), 4.38, (s, 2H), 6.73-6.78 (m, 1H), 6.85-6.93 (m, 2H), 7.14 (t, $J = 7.6\text{Hz}$, 1H), 7.23-7.33 (m, 7H), 7.43 (d, $J = 8.0\text{Hz}$, 2H). Found: C, 58.49; H, 5.69; N, 8.58. $\text{C}_{29}\text{H}_{36}\text{N}_4\text{O} \times 1.8\text{CF}_3\text{CO}_2\text{H} \times 0.4\text{H}_2\text{O}$ has C, 58.52; H, 5.82; N, 8.37 %. $[\alpha]_{\text{D}} = -32.24\text{deg}$ [c 0.943, MeOH].

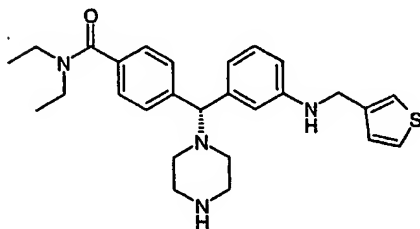
20

COMPOUND 8: N,N-diethyl-4-[(R)-{3-[(2-furylmethyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide



To a solution of INTERMEDIATE 5b (90 mg) in 1,2-dichloroethane (5 mL) was added 2-furaldehyde (18 μ L; 1.1 eq) and sodium triacetoxyborohydride (45 g; 1.1 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, trifluoroacetic acid (1 mL) was added to the reaction and stirred for 4 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 8 (35 mg, 31% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.09 (t, $J = 6.80\text{Hz}$, 3H), 1.21 (t, $J = 6.7\text{Hz}$, 3H), 2.58-2.65 (m, 4H), 3.19-3.26 (m, 6H), 3.51 (q, $J = 7.50\text{Hz}$, 2H), 4.38 (s, 2H), 4.39 (s, 1H), 6.23 (d, $J = 2.93\text{Hz}$, 1H), 6.31-6.34 (m, 1H), 6.75-6.79 (m, 1H), 6.96 (d, $J = 7.42\text{Hz}$, 2H), 7.17 (t, $J = 7.60\text{Hz}$, 1H), 7.31 (d, $J = 8.20\text{Hz}$, 2H), 7.44 (s, 1H), 7.52 (d, $J = 8.20\text{Hz}$, 2H). Found: C, 48.96; H, 4.90; N, 7.02. $\text{C}_{27}\text{H}_{34}\text{N}_4\text{O}_2 \times 3.0\text{CF}_3\text{CO}_2\text{H} \times 1.1\text{H}_2\text{O}$ has C, 49.03; H, 4.89; N, 6.93 %. $[\alpha]_{\text{D}} = -12.55\text{deg}$ [c 10.02, MeOH].

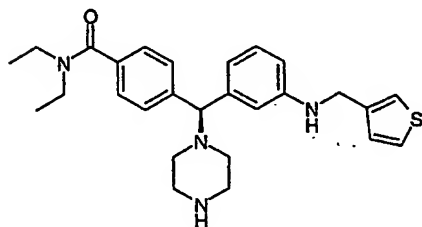
COMPOUND 9: N,N-diethyl-4-((R)-piperazin-1-yl){3-[(thien-3-ylmethyl)amino]phenyl}methyl)benzamide



To a solution of INTERMEDIATE 5b (90 mg) in 1,2-dichloroethane (5 mL) was added 3-thiophene carboxaldehyde (19 μ L; 1.1 eq) and sodium triacetoxyborohydride (45 g; 1.1 eq). The reaction was stirred at room temperature under nitrogen. After 18

hours, trifluoroacetic acid (1 mL) was added to the reaction and stirred for 4 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined
5 organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 9 (44 mg, 28% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral
10 HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.09 (t, $J = 6.68\text{Hz}$, 3H), 1.22 (t, $J = 6.68\text{Hz}$, 3H), 2.53-2.61 (m, 4H), 3.17-3.27 (m, 6H), 3.47-3.55 (m, 2H), 4.38 (s, 1H), 4.43 (s, 2H), 6.83-6.89 (m, 1H), 6.98-7.08 (m, 3H), 7.22 (t, $J = 7.68\text{Hz}$, 1H), 7.22-7.27 (m, 1H), 7.30 (d, $J = 8.35\text{Hz}$, 2H), 7.37 (dd, $J = 4.67, 3.24\text{Hz}$, 1H), 7.48 (d, $J = 8.01\text{Hz}$, 2H). Found: C, 51.83; H, 5.14; N, 7.78. $\text{C}_{27}\text{H}_{34}\text{N}_4\text{OS} \times 2\text{CF}_3\text{CO}_2\text{H} \times 0.8\text{H}_2\text{O}$
15 has C, 51.81; H, 5.23; N, 7.70 %. $[\alpha]_D = -20.06\text{deg}$ [c 0.708, MeOH].

COMPOUND 10: N,N-diethyl-4-((S)-piperazin-1-yl{3-[(thien-3-ylmethyl)amino]phenyl)methyl)benzamide

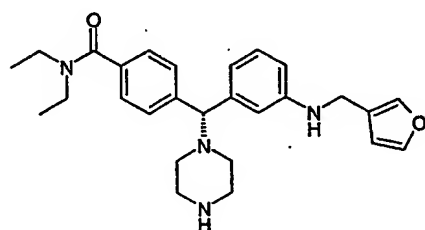


20

To a solution of INTERMEDIATE 5a (168 mg) in 1,2-dichloroethane (5 mL) was added 3-thiophene carboxaldehyde (34 μL ; 1.1 eq) and sodium triacetoxyborohydride (82 g; 1.1 eq). The reaction was stirred at room temperature under nitrogen. After 18
25 hours, trifluoroacetic acid (1 mL) was added to the reaction and stirred for 4 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined

organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography eluting with 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 10 (69 mg, 24% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.09 (t, J = 6.68Hz, 3H), 1.22 (t, J = 6.68Hz, 3H), 2.53-2.61 (m, 4H), 3.17-3.27 (m, 6H), 3.47-3.55 (m, 2H), 4.38 (s, 1H), 4.43 (s, 2H), 6.83-6.89 (m, 1H), 6.98-7.08 (m, 3H), 7.22 (t, J = 7.68Hz, 1H), 7.22-7.27 (m, 1H), 7.30 (d, J = 8.35Hz, 2H), 7.37 (dd, J = 4.67, 3.24Hz, 1H), 7.48 (d, J = 8.01Hz, 2H). Found: C, 49.26; H, 4.84; N, 7.24. C₂₇H₃₄N₄OS x 2.8CF₃CO₂H x 0.7H₂O has C, 49.28; H, 4.85; N, 7.05%. [α]_D²⁰ = + 13.98deg [c 0.615, MeOH].

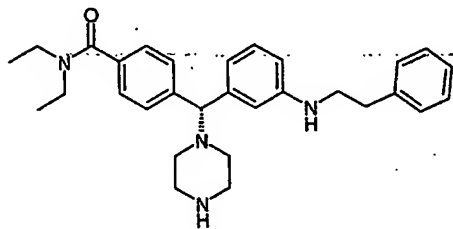
COMPOUND 11: N,N-diethyl-4-[(R)-{3-[(3-furylmethyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide



To a solution of INTERMEDIATE 5b (168 mg) in 1,2-dichloroethane (5 mL) was added 3-furaldehyde (34 μL; 1.1 eq) and sodium triacetoxyborohydride (82 g; 1.1 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, trifluoroacetic acid (1 mL) was added to the reaction and stirred for 4 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 11 (34 mg, 11% yield) as a colourless

solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.09 (t, J = 6.66Hz, 3H), 1.21 (t, J = 6.60Hz, 3H), 2.55-2.66 (m, 4H), 3.15-3.27(m, 6H), 3.47-3.55 (m, 2H), 4.18 (s, 2H), 4.33 (s, 1H), 6.37-6.39 (m, 1H), 6.64-6.68 (m, 1H), 6.81-6.87 (m, 3H), 7.11 (t, J = 7.65Hz, 1H), 7.30 (d, J = 8.65Hz, 2H), 7.38-7.43 (m, 1H), 7.51 (d, J = 7.98Hz, 2H). Found: C, 56.40; H, 5.39; N, 8.75. C₂₇H₃₄N₄O₂ x 1.8CF₃CO₂H x 1.0H₂O has C, 56.38; H, 5.54; N, 8.60 %. [α]_D²⁰ = -12.24deg [c 0.580, MeOH].

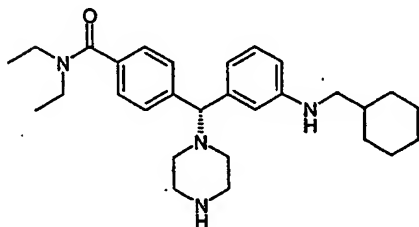
COMPOUND 12: N,N-diethyl-4-[(R)-{3-[(2-phenylethyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide



To a solution of INTERMEDIATE 5b (70 mg) in 1,2-dichloroethane (5 mL) was added phenyl acetaldehyde (253 μL/0.65 M in DCE; 1.1 eq) and sodium triacetoxyborohydride (35 g; 1.1 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, trifluoroacetic acid (1 mL) was added to the reaction and stirred for 4 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 12 (23 mg, 11% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.06 (t, J = 7.27Hz, 3H), 1.21 (t, J = 6.66Hz, 3H), 2.60-2.69 (m, 4H), 2.85 (t, J = 7.27Hz, 2H), 3.20-3.26 (m, 6H), 3.35 (t, J = 6.96Hz, 2H), 3.46-3.54 (m, 2H), 4.37 (s, 1H), 6.66-6.70 (m, 1H), 6.87-6.92 (m, 2H),

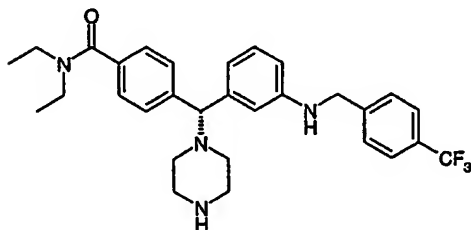
7.15 (t, $J = 7.88\text{Hz}$, 1H), 7.19 (s, 1H), 7.21 (s, 1H), 7.32 (d, $J = 8.17\text{Hz}$, 2H), 7.56 (d, $J = 8.17\text{Hz}$). Found: C, 58.72; H, 5.79; N, 8.25. $\text{C}_{30}\text{H}_{38}\text{N}_4\text{O} \times 1.9\text{CF}_3\text{CO}_2\text{H} \times 0.2\text{H}_2\text{O}$ has C, 58.76; H, 5.88; N, 8.11 %. $[\alpha]_{\text{D}} = -1\text{deg}$ [c 0.571, MeOH].

5 **COMPOUND 13:** 4-[(*R*)-{3-[(cyclohexylmethyl)amino]phenyl}(piperazin-1-yl)methyl]-*N,N*-diethylbenzamide



- 10 To a solution of INTERMEDIATE 5b (200 mg) in 1,2-dichloroethane (10 mL) was added cyclohexyl carboxaldehyde (57 μL ; 1.1 eq) and sodium triacetoxyborohydride (99 g; 1.1 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, trifluoroacetic acid (1 mL) was added to the reaction and stirred for 4 hours until complete removal of the boc group. The reaction was diluted with
- 15 dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained
- 20 as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 13 (37 mg, 11% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 0.98-1.06 (m, 2H), 1.06-1.11 (m, 4H), 1.17-1.26 (m, 6H), 1.58-1.68 (m, 1H), 1.72-1.84 (m, 4H), 2.65 (br s, 4H), 3.09 (d, $J = 6.85\text{Hz}$, 2H), 3.22-3.28 (m, 6H), 3.48-3.55 (m, 2H), 4.49 (s, 1H), 7.00-7.04 (m, 1H),
- 25 7.24-7.30 (m, 2H), 7.31-7.36 (m, 3H), 7.55 (d, $J = 8.17\text{Hz}$, 2H). $[\alpha]_{\text{D}}^{20} = -4.28\text{ deg}$ [c 0.864, MeOH].

COMPOUND 14: N,N-diethyl-4-[(R)-piperazin-1-yl(3-{[4-trifluoromethyl)benzyl]amino}phenyl)methyl]benzamide



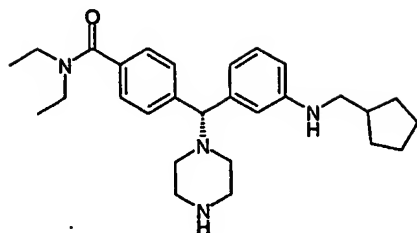
5

To a solution of INTERMEDIATE 5b (102 mg) in 1,2-dichloroethane (4 mL) was added 4-trifluoromethyl benzaldehyde (45 μ L; 1.5 eq) and sodium triacetoxymethylborohydride (70 g; 1.5 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, trifluoroacetic acid (0.5 mL) was added to the reaction

10 and stirred for 5 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 45%
 15 acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 14 (51 mg, 27% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.06 (t, J = 6.64Hz, 3H), 1.19 (t, J = 6.83Hz, 3H), 2.54-2.63 (m, 4H), 3.08-3.16 (m, 4H), 3.17-3.25 (m, 2H), 3.44-3.53 (m,
 20 2H), 4.23 (s, 1H), 4.39 (s, 2H), 6.49 (ddd, J = 8.15, 2.39, 0.98Hz, 1H), 6.61 (t, J = 1.85Hz, 1H), 6.63-6.67 (m, 1H), 7.00 (t, J = 7.81Hz, 1H), 7.22 (d, J = 8.32Hz, 2H), 7.39 (d, J = 8.20Hz, 2H), 7.49 (d, J = 8.01Hz, 2H), 7.57 (d, J = 8.21Hz, 2H). Found: C, 56.14; H, 5.49; N, 7.91. $\text{C}_{30}\text{H}_{35}\text{N}_4\text{O} \times 1.0\text{H}_2\text{O} \times 1.4\text{CF}_3\text{COOH}$ has C, 56.10; H, 5.51; N, 10.94%. $[\alpha]_{\text{D}}^{20} = -21.90$ deg [c 1.073, MeOH].

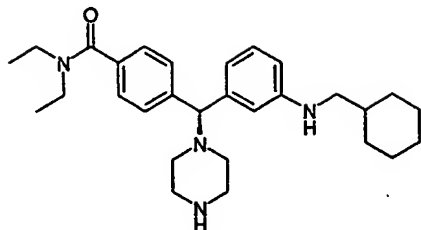
25

COMPOUND 15: 4-[(R)-{3-[(cyclopentylmethyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide



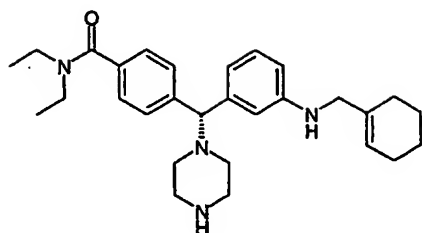
To a solution of INTERMEDIATE 5b (80 mg) in 1,2-dichloroethane (3 mL) was added cyclopentane carboxaldehyde (20 g; 1.5 eq) and sodium triacetoxyborohydride (51 g; 1.5 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, trifluoroacetic acid (0.5 mL) was added to the reaction and stirred for 5 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel, eluting 1%NH₄OH 10%MeOH in dichloromethane. The pure product was obtained and dissolved in dichloromethane in which 200μL of 1M HCl in ether was added. Solvent was removed and the product was isolated as the hydrochloride salt to give COMPOUND 15 (27 mg, 28% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.06 (t, J = 6.59Hz, 3H), 1.19 (t, J = 6.79Hz, 3H), 1.22-1.28 (m, 2H), 1.52-1.68 (m, 4H), 1.76-1.86 (m, 2H), 2.05-2.15 (m, 1H), 2.56-2.68 (m, 4H), 3.11 (d, J = 7.32Hz, 2H), 3.18-3.25 (m, 6H), 3.46-3.53 (m, 2H), 4.42 (s, 1H), 6.85-6.87 (m, 1H), 7.07-7.13 (m, 2H), 7.24 (t, J = 8.15Hz, 1H), 7.30 (d, J = 8.39Hz, 2H), 7.53 (d, J = 8.08Hz, 2H). Found: C, 53.18; H, 7.35; N, 8.26. C₂₈H₄₀N₄O x 2.4H₂O x 0.6HCl x 1.9CH₂Cl₂ has C, 53.19; H, 7.35; N, 8.06%. [α]_D²⁰ = -15.25deg [c 0.223, MeOH].

COMPOUND 16: 4-[(S)-{3-[(cyclohexylmethyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide



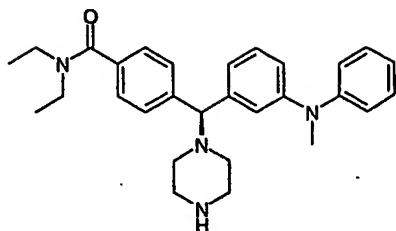
To a solution of INTERMEDIATE 5a (101 mg) in 1,2-dichloroethane (2 mL) was added cyclohexane carboxaldehyde (36 μ L; 1.5 eq) and sodium triacetoxyborohydride (67 g; 1.5 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, trifluoroacetic acid (0.5 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 40% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 16 (52 mg, 30% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 0.95-1.10 (m, 5H), 1.15-1.30 (m, 6H), 1.55-1.70 (m, 2H), 1.71-1.83 (m, 4H), 2.58-2.67 (m, 4H), 3.07 (d, $J = 6.93\text{Hz}$, 2H), 3.17-3.26 (m, 6H), 3.45-3.55 (m, 2H), 4.47 (s, 1H), 6.98-7.03 (m, 1H), 7.22-7.26 (m, 2H), 7.28-7.35 (m, 3H), 7.53 (d, $J = 8.10\text{Hz}$, 2H). Found: C, 52.34; H, 5.82; N, 7.13. $\text{C}_{29}\text{H}_{42}\text{N}_4\text{O} \times 0.7\text{H}_2\text{O} \times 2.8\text{CF}_3\text{COOH}$ has C, 52.30; H, 5.82; N, 7.13%. $[\alpha]_{\text{D}}^{20} = +4.07\text{deg}$ [c 0.639, MeOH].

COMPOUND 17: 4-[(R)-{3-[(cyclohex-1-en-1-ylmethyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide

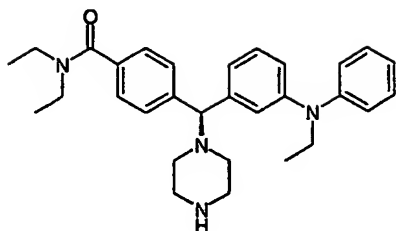


To a solution of INTERMEDIATE 5b (60 mg) in Methanol (2 mL) was added 1-cyclohexene carboxaldehyde (15 mg ; 1.1 eq) and decaborane (5 g; 0.3 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, the solvent was evaporated and the crude product dissolved in dichloromethane and trifluoroacetic acid (0.5 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 12% to 35% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 17 (25 mg, 24% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.06 (t, J = 5.57Hz, 3H), 1.19 (t, J = 6.64Hz, 3H), 1.48-1.55 (m, 2H), 1.55-1.63 (m, 2H), 1.89-2.00 (m, 4H), 2.56-2.66 (m, 4H), 3.17-3.25 (m, 6H), 3.39-3.53 (m, 2H), 3.68 (br s, 2H), 4.42 (s, 1H), 5.56 (br s, 1H), 6.83-6.88 (m, 1H), 7.08-7.13 (m, 2H), 7.23 (t, J = 8.01Hz, 1H), 7.30 (d, J = 8.45Hz, 2H), 7.53 (d, J = 8.15Hz, 2H). Found: C, 52.18; H, 5.37; N, 7.41. C₂₉H₄₀N₄O x 0.5H₂O x 2.9CF₃COOH has C, 52.23; H, 5.53; N, 7.00%. [α]_D²⁰ = -4.25deg [c 0.870, MeOH].

COMPOUND 18: N,N-diethyl-4-[(S)-{3-[methyl(phenyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide

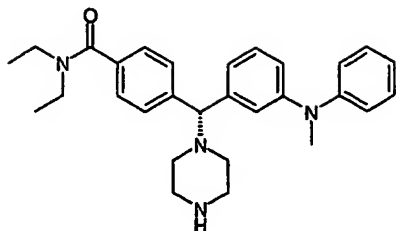


- To a solution of INTERMEDIATE 6a (225 mg) in methanol (3 mL) was added formaldehyde (67 μ L ; 2 eq) and decaborane (15 g; 0.3 eq). The reaction was stirred at room temperature under nitrogen and after 30 min the solution was concentrated. The residue was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added and the solution stirred for 18 hours until complete removal of the boc group. The reaction was concentrated and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by purified by flash chromatography on silica gel, eluting 1%NH₄OH 5%MeOH in dichloromethane. The pure product was obtained and dissolved in dichloromethane in which 650 μ L of 1M HCl in ether was added. Solvent was removed and the product was isolated as the hydrochloride salt to give COMPOUND 18 (99 mg, 52% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, d₆-DMSO) 1.00-1.16 (m, 6H), 2.25-2.37 (m, 4H), 2.76-2.86 (m, 4H), 3.10-3.22 (m, 2H), 3.24 (s, 3H), 3.35-3.43 (m, 2H), 4.30 (s, 1H), 6.83-6.86 (m, 1H), 6.63-7.00 (m, 4H), 7.10 (br s, 1H), 7.20 (t, J = 7.81Hz, 1H), 7.24-7.29 (m, 4H), 7.41 (d, J = 8.01Hz, 2H) [α]_D²⁰ = +0.97deg [c 0.310, MeOH].
- COMPOUND 19: N,N-diethyl-4-[(S)-{3-[ethyl(phenyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide

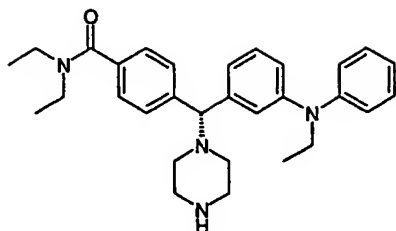


To a solution of INTERMEDIATE 6a (170 mg) in methanol (3 mL) was added acetaldehyde (3-4 mL) and decaborane (11 g; 0.3 eq). The reaction was stirred at 0°C and after 6 hours the solution was concentrated. The residue was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added and the solution stirred for 18 hours until complete removal of the boc group. The reaction was concentrated and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel, eluting 1%NH₄OH 5%MeOH in dichloromethane. The pure product was obtained and dissolved in dichloromethane in which 650μL of 1M HCl in ether was added. Solvent was removed and the product was isolated as the hydrochloride salt to give COMPOUND 19 (121 mg, 74% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.07 (t, J = 6.86Hz, 3H), 1.12 (t, J = 7.15Hz, 3H), 1.19 (t, J = 6.86Hz, 3H), 2.32-2.43 (m, 4H), 2.80-2.87 (m, 4H), 3.20-3.26 (m, 2H), 3.45-3.52 (m, 2H), 3.73 (q, J = 6.86Hz, 2H), 4.19 (s, 1H), 6.75 (ddd, J = 8.13, 2.47, 0.93Hz, 1H), 6.87-6.90 (m, 1H), 6.91-6.95 (m, 3H), 7.03 (t, J = 1.96Hz, 1H), 7.11 (t, J = 7.96Hz, 1H), 7.19-7.23 (m, 2H), 7.26 d, J = 8.28Hz, 2H), 7.45 (d, J = 8.50Hz, 2H).

COMPOUND 20: N,N-diethyl-4-[(R)-{3-[methyl(phenyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide

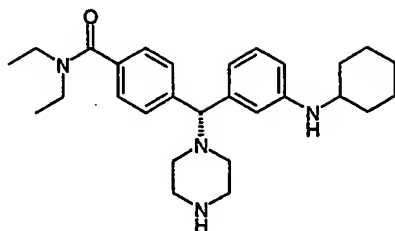


- To a solution of INTERMEDIATE 6b (170 mg) in methanol (3 mL) was added formaldehyde (45 μ L; 2 eq) and decaborane (11 g; 0.3 eq). The reaction was stirred at room temperature under nitrogen and after 30 min the solution was concentrated. The residue was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added and the solution stirred for 18 hours until complete removal of the boc group. The reaction was concentrated and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by purified by flash chromatography on silica gel, eluting 1% NH_4OH 5%MeOH in dichloromethane. The pure product was obtained and dissolved in dichloromethane in which 200 μ L of 1M HCl in ether was added. Solvent was removed and the product was isolated as the hydrochloride salt to give COMPOUND 20 (129 mg, 80% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, d_6 -DMSO) 1.00-1.16 (m, 6H), 2.25-2.37 (m, 4H), 2.76-2.86 (m, 4H), 3.10-3.22 (m, 2H), 3.24 (s, 3H), 3.35-3.43 (m, 2H), 4.30 (s, 1H), 6.83-6.86 (m, 1H), 6.63-7.00 (m, 4H), 7.10 (br s, 1H), 7.20 (t, $J = 7.81\text{Hz}$, 1H), 7.24-7.29 (m, 4H), 7.41 (d, $J = 8.01\text{Hz}$, 2H) $[\alpha]_D^{20} = +2.31\text{deg}$ [c.0.368, MeOH].
- COMPOUND 21: N,N-diethyl-4-[(R)-{3-[ethyl(phenyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide



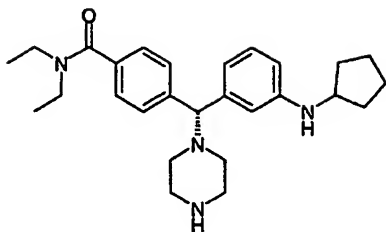
To a solution of INTERMEDIATE 6b (171 mg) in methanol (3 mL) was added acetaldehyde (3-4 mL) and decaborane (11 g; 0.3 eq). The reaction was stirred at 0°C and after 6 hours the solution was concentrated. The residue was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added and the solution stirred for 18 hours until complete removal of the boc group. The reaction was concentrated and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by purified by flash chromatography on silica gel, eluting 1%NH₄OH 5%MeOH in dichloromethane. The pure product was obtained and dissolved in dichloromethane in which 650μL of 1M HCl in ether was added. Solvent was removed and the product was isolated as the hydrochloride salt to give COMPOUND 21 (155 mg, 81% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.07 (t, J = 6.86Hz, 3H), 1.12 (t, J = 7.15Hz, 3H), 1.19 (t, J = 6.86Hz, 3H), 2.32-2.43 (m, 4H), 2.80-2.87 (m, 4H), 3.20-3.26 (m, 2H), 3.45-3.52 (m, 2H), 3.73 (q, J = 6.86Hz, 2H), 4.19 (s, 1H), 6.75 (ddd, J = 8.13, 2.47, 0.93Hz, 1H), 6.87-6.90 (m, 1H), 6.91-6.95 (m, 3H), 7.03 (t, J = 1.96Hz, 1H), 7.11 (t, J = 7.96Hz, 1H), 7.19-7.23 (m, 2H), 7.26 d, J = 8.28Hz, 2H), 7.45 (d, J = 8.50Hz, 2H).

COMPOUND 22: 4-[(R)-{3-[(cyclohexylmethyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide



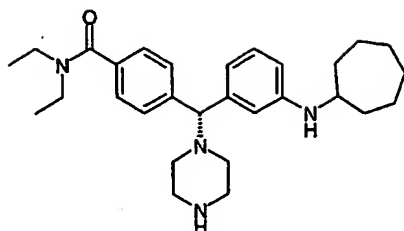
To a solution of INTERMEDIATE 5b (106 mg) in 1,2-dichloroethane (2 mL) was added cyclohexanone (35 μ L; 1.5 eq) and sodium triacetoxyborohydride (72 g; 1.5 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, the reaction was concentrated and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate and concentrated. The product was purified on silica gel eluting 30% acetone in hexane and pure fractions collected were concentrated. The resulting product was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added and the solution stirred for 18 hours until complete removal of the boc group. The reaction was concentrated and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 12% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 22 (41 mg, 23% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.06 (t, J = 7.42Hz, 3H), 1.19 (t, J = 6.93Hz, 3H), 1.22-1.39 (m, 5H), 1.62-1.69 (m, 1H), 1.76-1.83 (m, 2H), 1.84-1.94 (m, 2H), 2.58-2.67 (m, 4H), 3.17-3.26 (m, 6H), 3.32-3.39 (m, 1H), 3.45-3.52 (m, 2H), 4.54 (s, 1H), 7.14 (ddd, J = 7.61, 2.18, 1.16Hz, 1H), 7.32 (d, J = 8.44Hz, 2H), 7.43 (t, J = 7.66Hz, 2H), 7.45-7.49 (m, 1H), 7.53 (d, J = 8.19Hz). Found: C, 54.10; H, 6.13; N, 7.77. $\text{C}_{28}\text{H}_{40}\text{N}_4\text{O} \times 0.7\text{H}_2\text{O} \times 2.3\text{CF}_3\text{COOH}$ has C, 54.12; H, 6.09; N, 7.74%. $[\alpha]_{\text{D}}^{20} = -6.39$ deg [c 0.939, MeOH].

COMPOUND 23: 4-[(R)-[3-(cyclopentylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide



To a solution of INTERMEDIATE 5b (116 mg) in methanol (3 mL) was added
 5 cyclopentanone (24 μ L; 1.1 eq) and decaborane (10 g; 0.3 eq). The reaction was
 stirred at room temperature under nitrogen. After 18 hours, the solvent was
 evaporated and the crude product dissolved in dichloromethane and trifluoroacetic
 acid (0.5 mL) was added to the reaction and stirred for 18 hours until complete
 removal of the boc group. The reaction was diluted with dichloromethane and washed
 10 with saturated aqueous sodium bicarbonate. The aqueous was extracted with two
 portions of dichloromethane and the combined organics were dried over anhydrous
 sodium sulfate, filtered and concentrated. The residue was purified by reverse phase
 chromatography, eluting 10% to 35% acetonitrile in water containing 0.1%
 trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was
 15 lyophilized to give COMPOUND 23 (70 mg, 36% yield) as a colourless solid. Purity
 (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD)
 1.06 (t, J = 6.64Hz, 3H), 1.19 (t, J = 6.74Hz, 3H), 1.60-1.66 (m, 4H), 1.74-1.80 (m,
 2H), 1.90-1.96 (m, 2H), 2.60-2.66 (m, 4H), 3.18-3.27 (m, 6H), 3.45-3.52 (m, 2H),
 3.81-3.92 (m, 1H), 4.54 (s, 1H), 7.14 (dt, J = 7.32, 1.90Hz, 1H), 7.31 (d, J = 8.40Hz,
 20 2H), 7.38-7.46 (m, 3H), 7.53, (d, J = 8.20Hz, 2H). Found: C, 52.17; H, 5.68; N, 7.63.
 $\text{C}_{27}\text{H}_{38}\text{N}_4\text{O} \times 0.6\text{H}_2\text{O} \times 2.6\text{CF}_3\text{COOH}$ has C, 53.13; H, 5.68; N, 7.55%. $[\alpha]_{\text{D}}^{20} = -$
 7.44deg [c 0.806, MeOH].

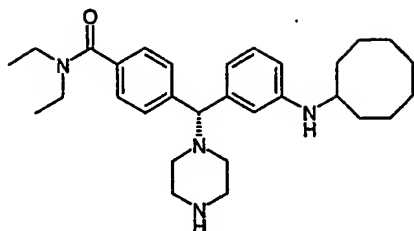
COMPOUND 24: 4-[(R)-[3-(cycloheptylamino)phenyl](piperazin-1-yl)methyl]-
 25 N,N-diethylbenzamide



To a solution of INTERMEDIATE 5b (95 mg) in methanol (3 mL) was added cycloheptanone (26 μ L; 1.1 eq) and decaborane (7.4 g; 0.3 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, the solvent was evaporated and the crude product dissolved in dichloromethane and trifluoroacetic acid (0.5 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 35% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 24 (55 mg, 34% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.06 (t, J = 6.54Hz, 3H), 1.19 (t, J = 6.64Hz, 3H), 1.40-1.49 (m, 2H), 1.53-1.63 (m, 6H), 1.65-1.75 (m, 2H), 1.89-1.97 (m, 2H), 2.60-2.66 (m, 4H), 3.18-3.26 (m, 6H), 3.45-3.52 (m, 2H), 3.52-3.59 (m, 1H), 4.54 (s, 1H), 7.13 (dt, J = 7.37, 1.68Hz, 1H), 7.31 (d, J = 8.40Hz, 2H), 7.38-7.47 (m, 3H), 7.53 (d, J = 8.20Hz, 2H). Found: C, 54.35; H, 5.98; N, 7.57. $\text{C}_{29}\text{H}_{42}\text{N}_4\text{O} \times 0.2\text{H}_2\text{O} \times 2.5\text{CF}_3\text{COOH}$ has C, 54.35; H, 6.02; N, 7.46%. $[\alpha]_{\text{D}}^{20} = -7.70^\circ$ [c 0.649, MeOH].

COMPOUND 25: 4-[(R)-[3-(cyclooctylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide

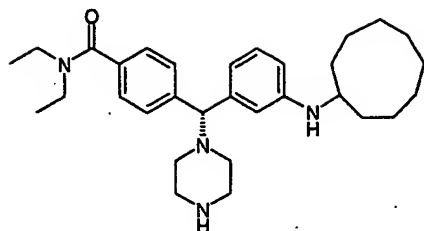
63



To a solution of INTERMEDIATE 5b (148 mg) in methanol (3 mL) was added cyclooctanone (48 g; 1.2 eq) and decaborane (11 g; 0.3 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, the solvent was evaporated and the crude product dissolved in dichloromethane and trifluoroacetic acid (0.5 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 15% to 35% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 25 (88 mg, 34% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.06 (t, J = 6.74Hz, 3H), 1.19 (t, J = 6.69Hz, 3H), 1.40-1.52 (m, 3H), 1.52-1.60 (m, 4H), 1.60-1.76 (m, 5H), 1.80-1.90 (m, 2H), 2.58-2.66 (m, 4H), 3.18-3.25 (m, 6H), 3.45-3.53 (m, 2H), 3.61-3.66 (m, 1H), 4.56 (s, 1H), 7.20 (ddd, J = 7.81, 2.15, 0.98Hz, 1H), 7.32 (d, J = 8.47Hz, 2H), 7.45 (t, J = 7.81Hz, 2H), 7.49 (br s, 1H), 7.51-7.55 (m, 3H). Found: C, 54.26; H, 6.10; N, 7.24. C₃₀H₄₄N₄O x 0.3H₂O x 2.6CF₃COOH has C, 54.30; H, 6.11; N, 7.20%. [α]_D²⁰ = -8.86deg [c 0.700, MeOH].

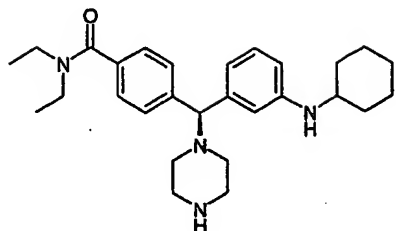
COMPOUND 26: 4-[(R)-[3-(cyclononylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide

25



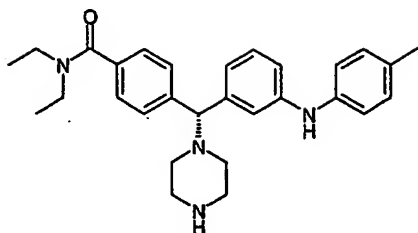
To a solution of INTERMEDIATE 5b (106 mg) in methanol (3 mL) was added cyclononanone (40 μ L; 1.2 eq) and decaborane (8 g; 0.3 eq). The reaction was stirred
5 at room temperature under nitrogen. After 18 hours, the reaction was concentrated and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate and concentrated. The product was purified on silica gel eluting 35% acetone in hexane and pure fractions collected were concentrated. The resulting product was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added and the solution
10 stirred for 18 hours until complete removal of the boc group. The reaction was concentrated and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase
15 chromatography, eluting 15% to 35% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 26 (64 mg, 34% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.00-1.10 (m, 3H), 1.15-1.23 (m, 3H), 1.31-1.45 (m, 4H), 1.45-1.55 (m, 6H), 1.55-
20 1.68 (m, 2H), 1.70-1.83 (m, 4H), 2.55-2.70 (m, 4H), 3.15-3.25 (m, 6H), 3.43-3.54 (m, 2H), 3.63-3.70 (m, 1H), 4.56 (s, 1H), 7.18-7.25 (m, 1H), 7.28-7.34 (m, 2H), 7.45-7.50 (m, 1H), 7.51-7.56 (m, 4H). Found: C, 54.34; H, 6.29; N, 7.06. $\text{C}_{31}\text{H}_{46}\text{N}_4\text{O} \times 0.7\text{H}_2\text{O} \times 2.6\text{CF}_3\text{COOH}$ has C, 54.36; H, 6.30; N, 7.01%. $[\alpha]_{\text{D}}^{20} = -10.40^\circ$ [c 0.625, MeOH].

25 **COMPOUND 27: 4-[(S)-[3-(cyclohexylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide**



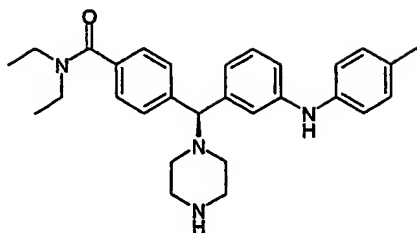
To a solution of INTERMEDIATE 5a (94 mg) in methanol (3 mL) was added cyclohexanone (23 μ L; 1.1 eq) and decaborane (7.4 g; 0.3 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, the solvent was evaporated and the crude product dissolved in dichloromethane and trifluoroacetic acid (0.5 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 12% to 40% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 27 (74 mg, 46% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.06 (t, J = 7.42Hz, 3H), 1.19 (t, J = 6.93Hz, 3H), 1.22-1.39 (m, 5H), 1.62-1.69 (m, 1H), 1.76-1.83 (m, 2H), 1.84-1.94 (m, 2H), 2.58-2.67 (m, 4H), 3.17-3.26 (m, 6H), 3.32-3.39 (m, 1H), 3.45-3.52 (m, 2H), 4.55 (s, 1H), 7.14 (ddd, J = 7.61, 2.18, 1.16Hz, 1H), 7.32 (d, J = 8.44Hz, 2H), 7.43 (t, J = 7.66Hz, 2H), 7.45-7.49 (m, 1H), 7.53 (d, J = 8.19Hz, 2H). Found: C, 53.79; H, 5.91; N, 7.66. $\text{C}_{28}\text{H}_{40}\text{N}_4\text{O} \times 0.2\text{H}_2\text{O} \times 2.5\text{CF}_3\text{COOH}$ has C, 53.76; H, 5.86; N, 7.60%. $[\alpha]_{\text{D}}^{20} = +7.44^\circ$ [c 0.632, MeOH].

COMPOUND 28: N,N-diethyl-4-[(R)-{3-[(4-methylphenyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide



To a solution of INTERMEDIATE 5b (108 mg) in toluene (2 mL) was added 4-bromo toluene (51 g; 1.3 eq), $\text{Pd}_2(\text{dba})_3$ (25 g; 0.04 eq), Sodium *tert*-butoxide (93 g; 1.4 eq) and BINAP (34 g; 0.08 eq). The solution was heated in the microwave in a sealed tube for 5 min at 110°C. The resulting mixture filtered through celite and concentrated. The crude was purified by a normal phase MPLC with a disposable silica gel column (40 g); eluting 40% to 60% ethyl acetate in hexane. Pure fraction collected and concentrated to afford yellow foam. The resulting product was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added and the solution stirred for 18 hours until complete removal of the boc group. The reaction was concentrated and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated to about 2 mL of solvent. In the solution was added 475 μL of 1M HCl in ether and the solvent were removed and the product was isolated as the hydrochloride salt to give COMPOUND 28 (62 mg, 59% yield) as beige solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.07 (t, $J = 6.88\text{Hz}$, 3H), 1.20 (t, $J = 6.83\text{Hz}$, 3H), 2.24 (s, 3H), 3.00-3.16 (m, 3H), 3.18-3.26 (m, 3H), 3.42-3.53 (m, 6H), 6.91 (br s, 1H), 6.93 (d, $J = 8.30\text{Hz}$, 2H), 7.00 (br s, 1H), 7.04 (d, $J = 8.29\text{Hz}$, 2H), 7.18 (t, $J = 7.91\text{Hz}$, 1H), 7.22 (br s, 1H), 7.39 (d, $J = 7.91\text{Hz}$, 2H), 7.72 (d, $J = 7.22\text{Hz}$, 2H). Found: C, 62.07; H, 6.92; N, 9.42. $\text{C}_{29}\text{H}_{36}\text{N}_4\text{O} \times 2.9\text{HCl} \times 0.3\text{C}_4\text{H}_{10}\text{O}$ has C, 62.05; H, 7.22 N, 9.58%. $[\alpha]_{\text{D}}^{20} = -4.04\text{deg}$ [c 0.339, MeOH].

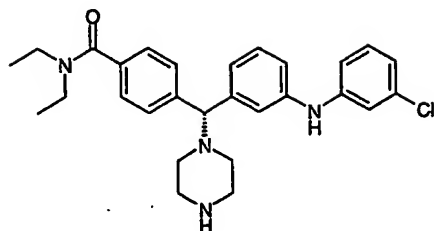
COMPOUND 29: N,N-diethyl-4-[(S)-{3-[(4-methylphenyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide



To a solution of INTERMEDIATE 5a (101 mg) in toluene (2 mL) was added 4-bromo
 toluene (48 g; 1.3 eq), Pd₂(dba)₃ (8.2 g; 0.04 eq), Sodium *tert*-butoxide (29 g; 1.4 eq)
 5 and BINAP (11 g; 0.08 eq). The solution was heated in the microwave in a sealed
 tube for 5 min at 110°C. The resulting mixture filtered through celite and
 concentrated. The crude was purified by a normal phase MPLC with a disposable
 silica gel column (40 g); eluting 40% to 60% ethyl acetate in hexane. Pure fraction
 collected and concentrated to afford yellow foam. The resulting product was dissolved
 10 in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added and the
 solution stirred for 18 hours until complete removal of the boc group. The reaction
 was concentrated and diluted with dichloromethane, washed with saturated aqueous
 sodium bicarbonate. The aqueous was extracted with two portions of
 dichloromethane and the combined organics were dried over anhydrous sodium
 15 sulfate, filtered and concentrated to about 2 mL of solvent. In the solution was added
 490 µL of 1M HCl in ether and the solvent was removed and the product was isolated
 as the hydrochloride salt to give COMPOUND 29 (67 mg, 68% yield) as beige solid.
 Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz,
 CD₃OD) 1.07 (t, J = 6.88Hz, 3H), 1.20 (t, J = 6.83Hz, 3H), 2.24 (s, 3H), 3.00-3.16 (m,
 20 3H), 3.18-3.26 (m, 3H), 3.42-3.53 (m, 6H), 6.91 (br s, 1H), 6.93 (d, J = 8.30Hz, 2H),
 7.00 (br s, 1H), 7.04 (d, J = 8.29Hz, 2H), 7.18 (t, J = 7.91Hz, 1H), 7.22 (br s, 1H),
 7.39 (d, J = 7.91Hz, 2H), 7.72 (d, J = 7.22Hz, 2H). Found: C, 61.50; H, 6.97; N, 9.43.
 C₂₉H₃₆N₄O x 0.1H₂O x 3.0HCl 0.3C₄H₁₀O has C, 61.47; H, 7.21; N, 9.50%. [α]_D²⁰ =
 +3.03deg [c 0.343, MeOH].

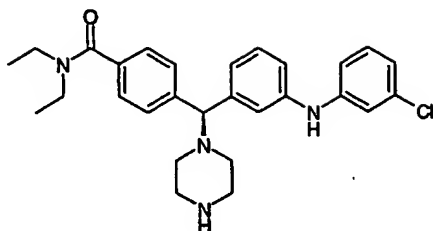
25

COMPOUND 30: 4-[(R)-{3-[(3-chlorophenyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide

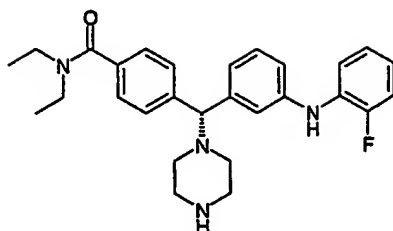


To a solution of INTERMEDIATE 5b (108 mg) in toluene (2 mL) was added 3-chloro-bromobenzene (35 μ L; 1.3 eq), $\text{Pd}_2(\text{dba})_3$ (8.2 g; 0.04 eq), Sodium *tert*-butoxide (31 g; 1.4 eq) and BINAP (11 g; 0.08 eq). The solution was heated in the microwave in a sealed tube for 5 min at 110°C. The resulting mixture filtered through celite and concentrated. The crude was purified by a normal phase MPLC with a disposable silica gel column (40 g); eluting 40% to 60% ethyl acetate in hexane. Pure fraction collected and concentrated to afford yellow foam. The resulting product was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added and the solution stirred for 18 hours until complete removal of the boc group. The reaction was concentrated and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated to about 2 mL of solvent. In the solution was added 560 μ L of 1M HCl in ether and the solvent was removed and the product was isolated as the hydrochloride salt to give COMPOUND 30 (77 mg, 70% yield) as beige solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.07 (t, $J = 6.40\text{Hz}$, 3H), 1.20 (t, $J = 6.64\text{Hz}$, 3H), 3.05-3.27 (m, 6H), 3.43-3.57 (m, 6H), 6.80 (dd, $J = 8.01, 1.27\text{Hz}$, 1H), 6.92 (dd, $J = 8.15, 1.51\text{Hz}$, 1H), 6.99 (t, $J = 2.00\text{Hz}$, 1H), 7.00-7.04 (m, 1H), 7.13-7.17 (m, 2H), 7.27 (t, $J = 7.76\text{Hz}$, 1H), 7.39 (br s, 1H), 7.41 (d, $J = 7.81\text{Hz}$, 2H), 7.75 (d, $J = 6.74\text{Hz}$, 2H). Found: C, 58.16; H, 6.39; N, 9.10. $\text{C}_{28}\text{H}_{33}\text{N}_4\text{OCl} \times 2.9\text{HCl} \times 0.40\text{C}_4\text{H}_{10}\text{O}$ has C, 58.05; H, 6.57; N, 9.15%. $[\alpha]_{\text{D}}^{20} = -17.37\text{deg}$ [c 0.499, MeOH].

COMPOUND 31: 4-[(S)-{3-[(3-chlorophenyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide

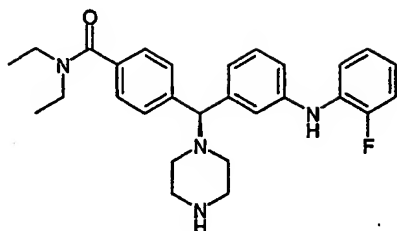


- To a solution of INTERMEDIATE 5a (103 mg) in toluene (2 mL) was added 3-chloro-bromobenzene (34 μ L; 1.3 eq), $\text{Pd}_2(\text{dba})_3$ (8.2 g; 0.04 eq), Sodium *tert*-butoxide (29 g; 1.4 eq) and BINAP (11 g; 0.08 eq). The solution was heated in the microwave in a sealed tube for 5 min at 110°C. The resulting mixture filtered through celite and concentrated. The crude was purified by a normal phase MPLC with a disposable silica gel column (40 g); eluting 40% to 60% ethyl acetate in hexane. Pure fraction collected and concentrated to afford yellow foam. The resulting product was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added and the solution stirred for 18 hours until complete removal of the boc group. The reaction was concentrated and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated to about 2 mL of solvent. In the solution was added 560 μ L of 1M HCl in ether and the solvent was removed and the product was isolated as the hydrochloride salt to give COMPOUND 30 (77 mg, 73% yield) as beige solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.07 (t, $J = 6.40\text{Hz}$, 3H), 1.20 (t, $J = 6.64\text{Hz}$, 3H), 3.05-3.27 (m, 6H), 3.43-3.57 (m, 6H), 6.80 (dd, $J = 8.01, 1.27\text{Hz}$, 1H), 6.92 (dd, $J = 8.15, 1.51\text{Hz}$, 1H), 6.99 (t, $J = 2.00\text{Hz}$, 1H), 7.00-7.04 (m, 1H), 7.13-7.17 (m, 2H), 7.27 (t, $J = 7.76\text{Hz}$, 1H), 7.39 (br s, 1H), 7.41 (d, $J = 7.81\text{Hz}$, 2H), 7.75 (d, $J = 6.74\text{Hz}$, 2H). $[\alpha]_D^{20} = +20.77^\circ$ [c 0.467, MeOH].
- COMPOUND 32: 4-[(R)-{3-[(2-fluorophenyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide



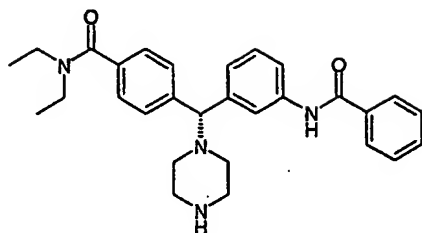
To a solution of INTERMEDIATE 5b (131 mg) in toluene (2 mL) was added 2-fluoro-bromobenzene (40 μ L; 1.3 eq), $\text{Pd}_2(\text{dba})_3$ (10 g; 0.04 eq), Sodium *tert*-butoxide (37 g; 1.4 eq) and BINAP (13 g; 0.08 eq). The solution was heated in the microwave in a sealed tube for 5 min at 110°C. The resulting mixture filtered through celite and concentrated. The crude was purified by a normal phase MPLC with a disposable silica gel column (40 g); eluting 40% to 60% ethyl acetate in hexane. Pure fraction collected and concentrated to afford yellow foam. The resulting product was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added and the solution stirred for 18 hours until complete removal of the boc group. The reaction was concentrated and diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated to about 2 mL of solvent. In the solution was added 631 μ L of 1M HCl in ether and the solvent was removed and the product was isolated as the hydrochloride salt to give COMPOUND 32 (83 mg, 64% yield) as beige solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.07 (t, $J = 6.25\text{Hz}$, 3H), 1.20 (t, $J = 7.08\text{Hz}$, 3H), 3.05-3.17 (m, 2H), 3.18-3.25 (m, 4H), 3.40-3.55 (m, 6H), 6.87-6.96 (m, 2H), 7.01-7.06 (m, 1H), 7.06-7.14 (m, 2H), 1.18-7.25 (m, 3H), 7.40 (d, $J = 7.81\text{Hz}$, 2H), 7.74 (d, $J = 7.13\text{Hz}$, 2H). Found: C, 59.59; H, 6.56; N, 9.29. $\text{C}_{28}\text{H}_{33}\text{FN}_4\text{O} \times 2.9\text{HCl} \times 0.4\text{C}_4\text{H}_{10}\text{O}$ has C, 59.65; H, 6.75; N, 9.40%. $[\alpha]_{\text{D}}^{20} = +2.59\text{deg}$ [c 0.617, MeOH].

COMPOUND 33: 4-[(S)-{3-[(2-fluorophenyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide



To a solution of INTERMEDIATE 5a (99 mg) in toluene (2 mL) was added 2-fluoro-
 bromobenzene (30 μ L; 1.3 eq), $\text{Pd}_2(\text{dba})_3$ (7 g; 0.04 eq), Sodium *tert*-butoxide (28 g;
 5 1.4 eq) and BINAP (11 g; 0.08 eq). The solution was heated in the microwave in a
 sealed tube for 5 min at 110°C. The resulting mixture filtered through celite and
 concentrated. The crude was purified by a normal phase MPLC with a disposable
 silica gel column (40 g); eluting 40% to 60% ethyl acetate in hexane. Pure fraction
 collected and concentrated to afford yellow foam. The resulting product was dissolved
 10 in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added and the
 solution stirred for 18 hours until complete removal of the boc group. The reaction
 was concentrated and diluted with dichloromethane, washed with saturated aqueous
 sodium bicarbonate. The aqueous was extracted with two portions of
 dichloromethane and the combined organics were dried over anhydrous sodium
 15 sulfate, filtered and concentrated to about 2 mL of solvent. In the solution was added
 460 μ L of 1M HCl in ether and the solvent was removed and the product was isolated
 as the hydrochloride salt to give COMPOUND 33 (61 mg, 63% yield) as beige solid.
 Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz,
 CD_3OD) 1.07 (t, $J = 6.25\text{Hz}$, 3H), 1.20 (t, $J = 7.08\text{Hz}$, 3H), 3.05-3.17 (m, 2H), 3.18-
 20 3.25 (m, 4H), 3.40-3.55 (m, 6H), 6.87-6.96 (m, 2H), 7.01-7.06 (m, 1H), 7.06-7.14 (m,
 2H), 1.18-7.25 (m, 3H), 7.40 (d, $J = 7.81\text{Hz}$, 2H), 7.74 (d, $J = 7.13\text{Hz}$, 2H). Found: C,
 59.14; H, 6.51; N, 9.41. $\text{C}_{29}\text{H}_{42}\text{N}_4\text{O} \times 3.0\text{HCl} \times 0.3\text{C}_4\text{H}_{10}\text{O}$ has C, 59.22; H, 6.64; N,
 9.46%. $[\alpha]_{\text{D}}^{20} = +4.26\text{deg}$ [c 0.329, MeOH].

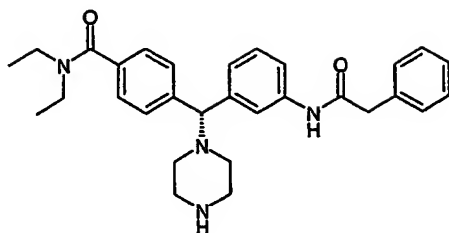
25 COMPOUND 34 4-[(R)-[3-(benzoylamino)phenyl](piperazin-1-yl)methyl]-N,N-
 diethylbenzamide



To a solution of INTERMEDIATE 5b (150 mg) in dichloromethane (10 mL) was added benzoic anhydride (80 g; 1.1 eq) and triethylamine (139 μ L; 3.1 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, trifluoroacetic acid (1 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 40% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 34 (110 mg, 49% yield) as a colourless solid. Purity (HPLC): > 98%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.08 (t, $J = 7.27\text{Hz}$, 3H), 1.21 (t, $J = 6.62\text{Hz}$, 3H), 2.6-2.73 (m, 4H), 3.21-3.28 (m, 6H), 3.46-3.54 (m, 2H), 4.49 (s, 1H), 7.21-7.25 (m, 1H), 7.30 (d, $J = 8.07\text{Hz}$, 1H), 7.34 (d, $J = 8.57\text{Hz}$, 2H), 7.42-7.47 (m, 1H), 7.47-7.53 (m, 3H), 7.55-7.61 (m, 3H), 7.88-7.92 (m, 2H), 7.99-8.02 (m, 1H). Found: C, 57.77; H, 5.61; N, 8.61. $\text{C}_{29}\text{H}_{34}\text{N}_4\text{O}_2 \times 1.6 \text{ CF}_3\text{CO}_2\text{H} \times 0.9 \text{ H}_2\text{O}$ has C, 57.79; H, 5.63; N, 8.37 %. $[\alpha]_{\text{D}}^{20} = -27.83\text{deg}$ [c 0.873, MeOH].

COMPOUND 35: N,N-diethyl-4-[(R)-{3-[(phenylacetyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide

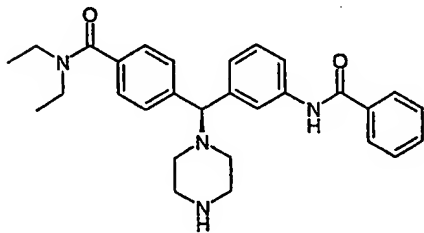
73



To a solution of INTERMEDIATE 5b (120 mg) in dichloromethane (8 mL) was added phenyl acetylchloride (41 μ L; 1.2 eq) and triethylamine (43 μ L; 1.2 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, the trifluoroacetic acid (1 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 40% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 35 (46 mg, 25% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; $^1\text{H NMR}$ (400MHz, CD_3OD) 1.05 (t, $J = 6.81\text{Hz}$, 3H), 1.19 (t, $J = 6.80\text{Hz}$, 3H), 2.50-2.67 (m, 4H), 3.16-3.25 (m, 6H), 3.44-3.52 (m, 2H), 3.63 (s, 2H), 4.41 (s, 1H), 7.12-7.16 (m, 1H), 7.19-7.26 (m, 3H), 7.26-7.33 (m, 6H), 7.52 (d, $J = 7.85\text{Hz}$, 2H), 7.84-7.87 (m, 1H). Found: C, 60.56; H, 6.08; N, 8.65. $\text{C}_{30}\text{H}_{36}\text{N}_4\text{O}_2 \times 2.4 \text{ H}_2\text{O} \times 0.9 \text{ CF}_3\text{COOH}$ has C, 60.58; H, 6.67; N, 8.89 %. $[\alpha]_{\text{D}}^{20} = -17.21 \text{ deg}$ [c 0.825, MeOH].

20

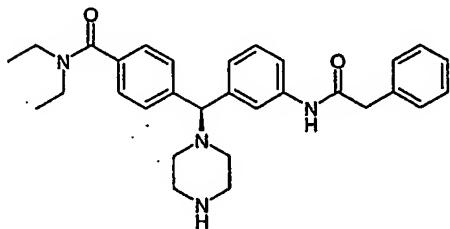
COMPOUND 36: 4-[(S)-[3-(benzoylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide



To a solution of INTERMEDIATE 5a (111 mg) in pyridine (3 mL) was added benzoyl chloride (31 g; 1.2 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, reaction was concentrated and the crude dissolved in
5 dichloromethane and trifluoroacetic acid (1 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The
10 residue was purified by reverse phase chromatography, eluting 10% to 40% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 36 (100 mg, 60% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.06 (t, J = 6.74Hz, 3H), 1.19 (t, J =
15 6.74Hz, 3H), 2.87-2.99 (m, 4H), 3.18-3.25 (m, 2H), 3.36-3.42 (m, 4H), 3.46-3.53 (m, 2H), 7.33-7.38 (m, 4H), 7.46-7.51 (m, 2H), 7.52-7.58 (m, 2H), 7.69 (d, J = 8.10Hz, 2H), 7.88-7.92 (m, 2H), 8.02-8.04 (m, 1H). Found: C, 54.19; H, 5.55; N, 7.85. C₂₉H₃₄N₄O₂ x 2.2H₂O x 1.9CF₃COOH has C, 54.20; H, 5.59; N, 7.71%. [α]_D²⁰ = +16.30deg [c 1.550, MeOH].

20

COMPOUND 37: N,N-diethyl-4-[(S)-{3-[(phenylacetyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide

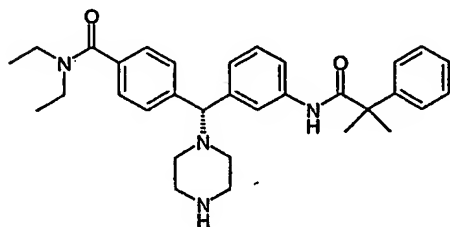


25

To a solution of INTERMEDIATE 5a (101 mg) in dichloromethane (8 mL) was added phenyl acetylchloride (34 μL; 1.2 eq) and triethylamine (57 μL; 2 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, the

trifluoroacetic acid (0.5 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 12% to 35% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 37 (67 mg, 43% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.05 (t, J = 6.74Hz, 3H), 1.19 (t, J = 6.69Hz, 3H), 2.52-2.65 (m, 4H), 3.17-3.25 (m, 6H), 3.45-3.53 (m, 2H), 3.63 (s, 2H), 4.41 (s, 1H), 7.13 (dt, J = 7.03, 1.71Hz, 1H), 7.19-7.26 (m, 3H), 7.26-7.32 (m, 5H), 7.51 (d, J = 8.20Hz, 2H), 7.85-7.87 (m, 1H). Found: C, 57.21; H, 5.71; N, 7.95. C₃₀H₃₆N₄O₂ x 0.9H₂O x 1.8CF₃COOH has C, 57.15; H, 5.65; N, 7.93%. [α]_D²⁰ = +21.60deg [c 0.375, MeOH].

COMPOUND 38: N,N-diethyl-4-[(R)-{3-[(2-methyl-2-phenylpropanoyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide



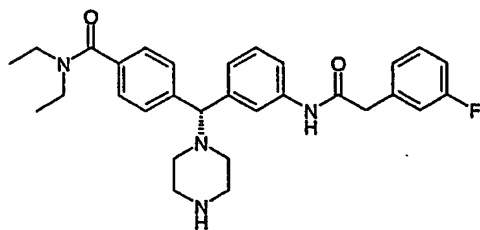
20

To a solution of INTERMEDIATE 5b (105 mg) in dimethylformamide (4 mL) was added α,α-dimethylphenylacetic acid (74 g; 2 eq), HATU (156 g; 4eq) and N,N-diisopropylethylamine (173 μL; 4eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, the reaction was concentrated and the crude dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined

organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 38 (51 mg, 5 31% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.06 (t, $J = 7.66\text{Hz}$, 3H), 1.19 (t, $J = 6.92\text{Hz}$, 3H), 1.58 (s, 6H), 2.53-2.68 (m, 4H), 3.17-3.25 (m, 6H), 3.44-3.53 (m, 2H), 4.40 (s, 1H), 7.11-7.17 (m, 1H), 7.18-7.24 (m, 3H), 7.29 (d, $J = 8.34\text{Hz}$, 2H), 7.31-7.38 (m, 4H), 7.52 (d, $J = 8.22\text{Hz}$, 2H), 7.71-7.73 (m, 1H). Found: C, 60.46; H, 6.23; 10 N, 8.18. $\text{C}_{32}\text{H}_{40}\text{N}_4\text{O}_2 \times 0.6\text{H}_2\text{O} \times 1.5\text{CF}_3\text{COOH}$ has C, 60.53; H, 6.20; N, 8.07%. $[\alpha]_{\text{D}}^{20} = -8.58$ deg [c 0.792, MeOH].

COMPOUND 39: N,N-diethyl-4-[(R)-(3-[[[3-
fluorophenyl)acetyl]amino}phenyl)(piperazin-1-yl)methyl]benzamide

15

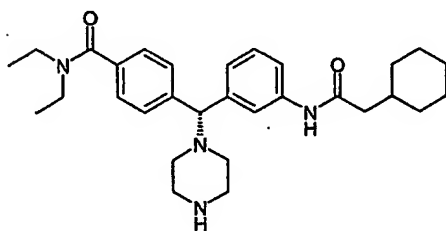


To a solution of INTERMEDIATE 5b (105 mg) in dimethylformamide (4 mL) was added 3-fluoro-phenylacetic acid (76 g; 2 eq), HATU (141 g; 1.5eq) and N,N- 20 diisopropylethylamine (173 μL ; 4eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, the DMF was concentrated and the crude dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. 25 The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained

as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 39 (91 mg, 50% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.05 (t, $J = 6.70\text{Hz}$, 3H), 1.19 (t, $J = 6.71\text{Hz}$, 3H), 2.50-2.69 (m, 4H), 3.15-3.25 (m, 6H), 3.44-3.53 (m, 2H), 3.65 (s, 2H), 4.41 (s, 1H), 6.96 (td, $J = 8.59, 2.73\text{Hz}$, 1H), 7.05-7.12 (m, 1H), 7.12-7.17 (m, 2H), 7.23 (t, $J = 7.85\text{Hz}$, 1H), 7.25 (t, $J = 1.80\text{Hz}$, 1H), 7.29 (d, $J = 8.34\text{Hz}$, 2H), 7.28-7.34 (m, 1H), 7.52 (d, $J = 8.34\text{Hz}$, 2H), 7.86 (t, $J = 1.65\text{Hz}$, 1H). Found: C, 57.56; H, 5.65; N, 8.21. $\text{C}_{30}\text{H}_{35}\text{N}_4\text{O}_2\text{F} \times 1.2\text{H}_2\text{O} \times 1.4\text{CF}_3\text{COOH}$ has C, 57.61; H, 5.72; N, 8.19%. $[\alpha]_{\text{D}}^{20} = -23.52 \text{ deg} \cdot [\text{c } 0.863, \text{MeOH}]$.

10

COMPOUND 40: 4-[(R)-{3-[(cyclohexylacetyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide



15

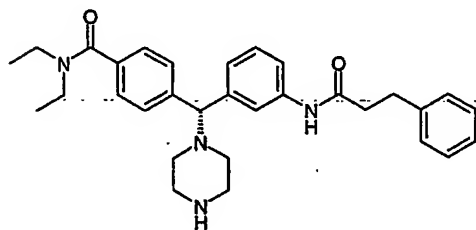
To a solution of INTERMEDIATE 5b (96 mg) in dimethylformamide (4 mL) was added cyclohexylacetic acid (58 g; 2 eq), HATU (117 g; 1.5eq) and N,N-diisopropylethylamine (143 μL ; 4eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, the reaction was concentrated and the crude dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 40 (59 mg, 40% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral

20

25

HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 0.95-1.03 (m, 2H), 1.03-1.08 (m, 3H), 1.16-1.21 (m, 3H), 1.22-1.32 (m, 2H), 1.61-1.76 (m, 6H), 1.76-1.85 (m, 1H), 2.19 (d, J = 7.14Hz, 2H), 2.55-2.67 (m, 4H), 3.18-3.25 (m, 6H), 3.45-3.52 (m, 2H), 4.42 (s, 1H), 7.14 (dt, J = 7.18, 1.59Hz, 1H), 7.21 (t, J = 7.66Hz, 1H), 7.25 (dt, J = 8.02, 1.96Hz, 1H), 7.30 (d, J = 8.20Hz, 2H), 7.53 (d, J = 8.30Hz, 2H). [α]_D²⁰ = -14.43deg [c 0.420, MeOH].

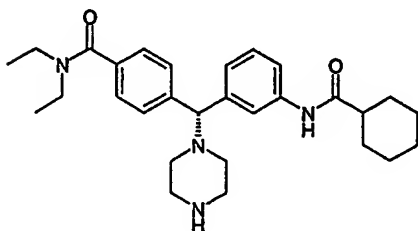
COMPOUND 41: N,N-diethyl-4-[(R)-{3-[(3-phenylpropanoyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide



To a solution of INTERMEDIATE 5b (128 mg) in dimethylformamide (3 mL) was added hydrocinammic acid (49 g; 1.2 eq), HATU (156 g; 1.5eq) and N,N-diisopropylethylamine (190 μL; 4eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, the reaction was concentrated and the crude dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified twice by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 41 (24 mg, 12% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.06 (t, J = 6.64Hz, 3H), 1.19 (t, J = 6.88Hz, 3H), 2.61 (t, J = 7.66Hz, 2H), 2.56-2.67 (m, 4H), 2.95 (t, J = 7.66Hz, 2H), 3.18-3.26 (m, 6H), 3.45-3.53 (m, 2H), 4.41 (s, 1H), 7.13-7.16 (m, 2H), 7.19-7.24 (m,

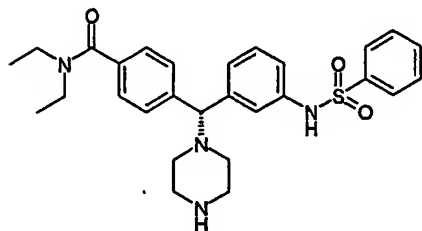
6H), 7.30 (d, J = 8.30Hz, 2H), 7.52 (d, J = 8.20Hz, 2H). $[\alpha]_D^{20} = -14.34^{\circ}$ [c 0.442, MeOH].

COMPOUND 42: 4-[(R)-{3-[(cyclohexylcarbonyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide



To a solution of INTERMEDIATE 5b (150 mg) in dimethylformamide (5 mL) was added cyclohexanecarboxylic acid (50 g; 1.2 eq), HATU (182 g; 1.5eq) and N,N-diisopropylethylamine (222 μ L; 4eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, the reaction was concentrated and the crude dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 42 (41 mg, 18% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.06 (t, J = 6.83Hz, 3H), 1.19 (t, J = 3.83Hz, 3H), 1.25-1.37 (m, 2H), 1.42-1.54 (m, 2H), 1.66-1.73 (m, 1H), 1.76-1.86 (m, 5H), 2.31 (tt, J = 11.69, 3.25Hz, 1H), 2.55-2.67 (m, 4H), 3.20-3.25 (m, 6H), 3.45-3.53 (m, 2H), 4.41 (s, 1H), 7.11-7.14 (m, 1H), 7.19-7.24 (m, 2H), 7.30 (d, J = 8.20Hz, 2H), 7.52 (d, J = 8.20Hz, 2H), 7.87 (s, 1H). $[\alpha]_D^{20} = -21.39^{\circ}$ [c 0.345, MeOH].

**COMPOUND 43: N,N-diethyl-4-[(R)-{3-
[(phenylsulfonyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide**

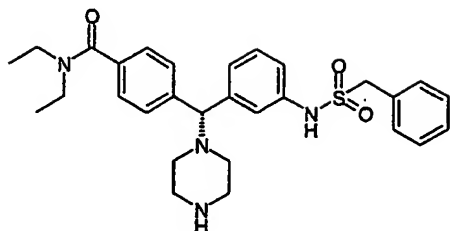


5

To a solution of INTERMEDIATE 5b (110 mg) in dichloromethane (10 mL) was added benzene sulfonyl chloride (33 μ L; 1.1 eq) and triethylamine (108 μ L; 3.3 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, the trifluoroacetic acid (1 mL) was added to the reaction and stirred for 18 hours until
10 complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 40% acetonitrile in water containing
15 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 43 (60 mg, 35% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.06 (t, J = 6.44Hz, 3H), 1.20 (t, J = 6.44Hz, 3H), 2.47-2.57 (m, 2H), 3.14-3.25 (m, 6H), 3.43, 3.53 (m, 2H), 4.34 (s, 1H), 6.81-6.86 (m, 1H), 7.06-7.14
20 (m, 2H), 7.25-7.32 (m, 3H), 7.36-7.44 (m, 4H), 7.48-7.55 (m, 1H), 7.06-7.65 (m, 2H). Found: C, 53.38; H, 5.29; N, 8.22. $\text{C}_{28}\text{H}_{34}\text{N}_4\text{O}_3\text{S} \times 1.6 \text{ CF}_3\text{CO}_2\text{H} \times 0.7 \text{ H}_2\text{O}$ has C, 53.40; H, 5.31; N, 7.98 %. $[\alpha]_{\text{D}}^{20} = -7.45$ deg [c 0.845, MeOH].

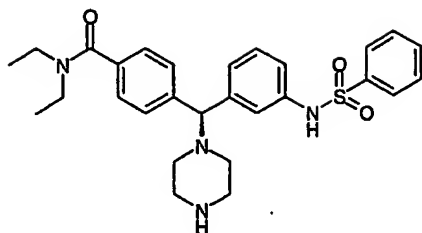
COMPOUND 44: 4-[(R)-{3-[(benzylsulfonyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide

25



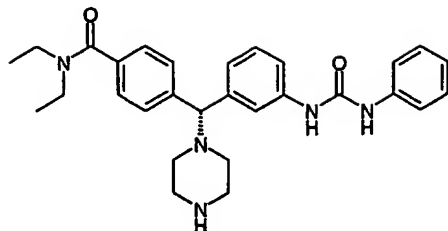
To a solution of INTERMEDIATE 5b (82 mg) in pyridine (3 mL) was added α -toluene sulfonyl chloride (40 g; 1.2 eq). The reaction was stirred at room temperature
5 under nitrogen. After 18 hours, reaction was concentrated and the crude product dissolved in dichloromethane (10 mL) and trifluoroacetic acid (1 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the
10 combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 40% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 44 (47 mg, 36% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity
15 (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.01 (t, $J = 6.91\text{Hz}$, 3H), 1.18 (t, $J = 6.75\text{Hz}$, 3H), 2.56-2.66 (m, 4H), 3.15-3.26 (m, 6H), 3.43-3.52 (m, 2H), 4.29 (s, 2H), 4.42 (s, 1H), 6.96 (ddd, $J = 7.96, 2.25, 1.12\text{Hz}$, 1H), 7.12-7.16 (m, 3H), 7.19-7.28 (m, 4H), 7.31-7.35 (m, 3H), 7.53 (d, $J = 8.02\text{Hz}$, 2H). Found: C, 55.53; H, 5.52; N, 8.11. $\text{C}_{29}\text{H}_{36}\text{N}_4\text{O}_3 \times 1.1\text{H}_2\text{O} \times 0.6\text{CF}_3\text{COOH}$ has C, 55.57; H, 5.58; N, 7.95%.
20 $[\alpha]_{\text{D}}^{20} = -7.23\text{deg}$ [c 0.844, MeOH].

COMPOUND 45: N,N-diethyl-4-[(S)-{3-[(phenylsulfonyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide



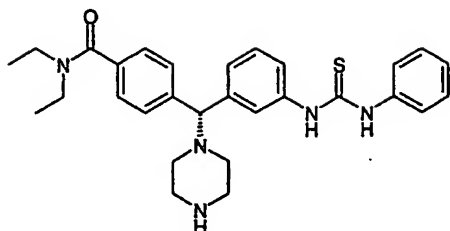
To a solution of INTERMEDIATE 5a (108 mg) in pyridine (2 mL) was added benzene sulfonyl chloride (38 μ L; 1.3 eq). The reaction was stirred at room temperature under nitrogen. After 18 hours, reaction was concentrated and the crude product dissolved in dichloromethane (5 mL) and trifluoroacetic acid (0.5 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 40% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 45 (86 mg, 50% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.06 (t, $J = 6.69\text{Hz}$, 3H), 1.20 (t, $J = 6.69\text{Hz}$, 3H), 2.46-2.56 (m, 4H), 3.15-3.26 (m, 6H), 3.45-3.53 (m, 2H), 4.35 (s, 1H), 6.83 (dt, $J = 7.59, 1.67\text{Hz}$, 1H), 7.05-7.08 (m, 1H), 7.11 (t, $J = 7.62\text{Hz}$, 1H), 7.28 (d, $J = 8.10\text{Hz}$, 2H), 7.29-7.32 (m, 1H), 7.34-7.43 (m, 4H), 7.47-7.53 (m, 1H), 7.61-7.65 (m, 2H). Found: C, 51.87; H, 5.04; N, 7.59. $\text{C}_{28}\text{H}_{34}\text{N}_4\text{O}_3\text{S} \times 0.7\text{H}_2\text{O} \times 1.9\text{CF}_3\text{COOH}$ has C, 51.90; H, 5.11; N, 7.61%. $[\alpha]_{\text{D}}^{20} = +6.43\text{deg}$ [c 0.917, MeOH].

COMPOUND 46: 4-[(R)-{3-[(anilinocarbonyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide



To a solution of INTERMEDIATE 5b (110 mg) in dichloromethane (3 mL) was added phenyl isocyanate (31 μ L; 1.2 eq) and triethylamine (1 drop). The reaction was stirred at room temperature under nitrogen. After 18 hours, trifluoroacetic acid (1 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 12% to 35% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 46 (64 mg, 38% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.06 (t, $J = 6.69\text{Hz}$, 3H), 1.19 (t, $J = 6.93\text{Hz}$, 3H), 2.55-2.67 (m, 4H), 3.20-3.26 (m, 6H), 3.44-3.51 (m, 2H), 4.42 (s, 1H), 6.99 (tt, $J = 7.37, 1.12\text{Hz}$, 1H), 7.05-7.11 (m, 2H), 7.20 (t, $J = 7.81\text{Hz}$, 1H), 7.22-7.28 (m, 2H), 7.30 (d, $J = 8.20\text{Hz}$, 2H), 7.38 (d, $J = 7.52\text{Hz}$, 2H), 7.55 (d, $J = 8.20\text{Hz}$, 2H), 7.76 (t, $J = 1.76\text{Hz}$, 1H). Found: C, 54.42; H, 5.28; N, 9.67. $\text{C}_{29}\text{H}_{35}\text{N}_5\text{O}_2 \times 0.8\text{H}_2\text{O} \times 2.0\text{CF}_3\text{COOH}$ has C, 54.44; H, 5.34; N, 9.62%. $[\alpha]_{\text{D}}^{20} = -28.95\text{deg}$ [c 0.836, MeOH].

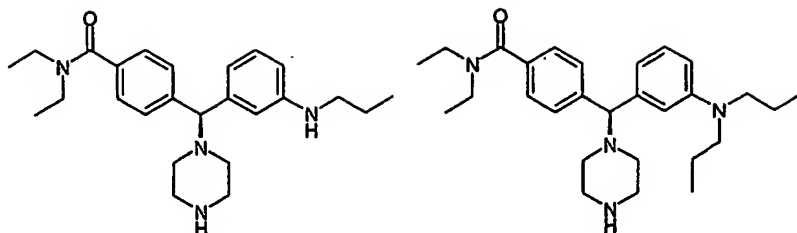
COMPOUND 47: 4-[(R)-{3-[(anilinocarbonothioyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide



To a solution of INTERMEDIATE 5b (115 mg) in dichloromethane (3 mL) was added phenyl isothiocyanate (35 μ L; 1.2 eq) and triethylamine (1 drop). The reaction was stirred at room temperature under nitrogen. After 18 hours, reaction was concentrated and purified by normal phase chromatography eluting with 35% acetone in hexane. The pure fractions were concentrated and dissolved in dichloromethane (10 mL) in which trifluoroacetic acid (1 mL) was added to the reaction and stirred for 18 hours until complete removal of the boc group. The reaction was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The aqueous was extracted with two portions of dichloromethane and the combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 12% to 35% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 48 (33 mg, 18% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.07 (t, J = 6.5Hz, 3H), 1.22 (t, J = 6.8Hz, 3H), 2.54-2.81 (m, 3H), 3.18-3.29 (m, 7H), 3.46-3.58 (m, 2H), 4.49 (s, 1H), 7.09-7.16 (m, 1H), 7.17-7.24 (m, 2H), 7.25-7.45 (m, 7H), 7.56 (d, J = 8.2Hz, 2H), 7.84 (t, J = 1.8Hz, 1H)

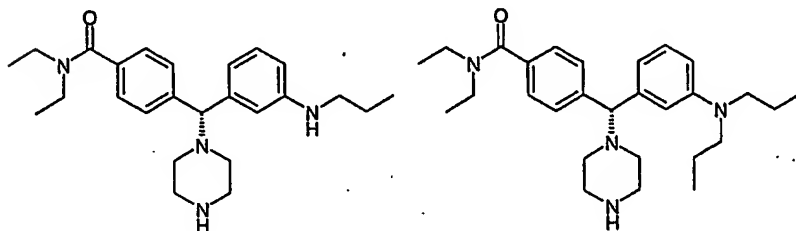
COMPOUND 48: *N,N*-diethyl-4-[(*S*)-1-piperazinyl][3-(propylamino)phenyl]methyl]benz-amide and COMPOUND 49: 4-[(*S*)-[3-(dipropylamino)phenyl]-1-piperazinylmethyl]-*N,N*-diethylbenzamide

85



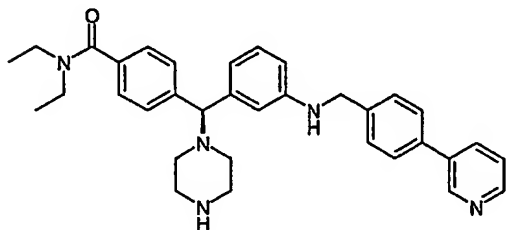
- Using the same method as for COMPOUND 17 and using INTERMEDIATE 5a (208 mg, 0.45 mmol), propionaldehyde (0.036 mL, 0.50 mmol), and decaborate (16.4 mg, 0.13 mmol) afforded COMPOUND 48 (174 mg, 52% yield) and COMPOUND 49 (43.5 mg, 12% yield) as their TFA salts. Each compound was lyophilized from CH₃CN/H₂O to produce colourless solids. COMPOUND 48: Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) δ 1.01 (t, J = 7.4Hz, 3H), 1.09 (br t, J = 6.7Hz, 3H), 1.22 (br t, J = 6.3Hz, 3H), 1.69 (sextet, J = 7.6Hz, 2H), 2.65 (br s, 4H), 3.20-3.29 (m, 8H), 3.52 (br q, J = 6.4Hz, 2H), 4.54 (s, 1H), 7.11-7.17 (m, 1H), 7.34 (d, J = 8.0Hz, 2H), 7.39-7.43 (m, 3H), 7.56 (d, J = 8.2Hz, 2H). Found: C, 51.41; H, 5.79; N, 7.98. C₂₅H₃₆N₄O x 0.8 H₂O x 2.4 CF₃COOH has C, 51.38; H, 5.79; N, 8.04%. [α]_D²⁰ = +7.18 deg [c 1.64, MeOH].
- COMPOUND 49: Purity (HPLC): > 82%; ¹H NMR (400MHz, CD₃OD) δ 0.83 (t, J = 7.3Hz, 6H), 1.04 (br t, J = 6.4Hz, 3H), 1.18 (br t, J = 6.5Hz, 3H), 1.30-1.44 (m, 4H), 2.63 (d, J = 5.1Hz, 4H), 3.14-3.28 (m, 6H), 3.43-3.52 (m, 6H), 4.59 (s, 1H), 7.31 (d, J = 8.2Hz, 2H), 7.36 (d, J = 7.4Hz, 1H), 7.47-7.58 (m, 4H), 7.66 (s, 1H).

- COMPOUND 50: *N,N*-diethyl-4-[(*R*)-1-piperazinyl]-3-(propylamino)phenyl]methyl]benz-amide and COMPOUND 51: 4-[(*R*)-[3-(dipropylamino)phenyl]-1-piperazinylmethyl]-*N,N*-diethylbenzamide



- Using the same method as for COMPOUND 17 and using INTERMEDIATE 5b (404 mg, 0.87 mmol), propionaldehyde (0.069 mL, 0.96 mmol), and decaborane (31.7 mg, 0.26 mmol) afforded COMPOUND 50 (217 mg, 34% yield) and COMPOUND 51 (128 mg, 19% yield) as their TFA salts. Each compound was lyophilized from CH₃CN/H₂O, producing COMPOUND 50 as a slightly yellow solid and COMPOUND 51 as a colourless solid. COMPOUND 50: Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) δ1.01 (t, J = 7.4Hz, 3H), 1.09 (br t, J = 6.8Hz, 3H), 1.22 (br t, J = 7.0Hz, 3H), 1.70 (sextet, J = 7.6Hz, 2H), 2.65 (br s, 4H), 3.20-3.29 (m, 8H), 3.52 (br q, J = 6.7Hz, 2H), 4.56 (s, 1H), 7.21 (ddd, J = 7.8, 2.3, 1.3Hz, 1H), 7.35 (d, J = 8.4Hz, 2H), 7.43-7.52 (m, 3H), 7.56 (d, J = 8.2Hz, 2H). Found: C, 46.23; H, 5.02; N, 6.58. C₂₅H₃₆N₄O x 1.0 H₂O x 3.6 CF₃COOH has C, 46.20; H, 5.01; N, 6.69%. [α]_D¹⁸ = -2.6 deg [c 0.657, MeOH].
- COMPOUND 51: Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) δ0.83 (t, J = 7.4Hz, 6H), 1.04 (br t, J = 6.6Hz, 3H), 1.18 (br t, J = 6.8Hz, 3H), 1.29-1.44 (m, 4H), 2.62 (d, J = 4.5Hz, 4H), 3.15-3.29 (m, 6H), 3.42-3.55 (m, 6H), 4.59 (s, 1H), 7.31 (d, J = 8.0Hz, 2H), 7.37 (d, J = 7.6Hz, 1H), 7.47-7.61 (m, 4H), 7.67 (s, 1H). Found: C, 45.63; H, 5.04; N, 6.21. C₂₈H₄₂N₄O x 1.5 H₂O x 4.2 CF₃COOH has C, 45.70; H, 5.18; N, 5.86%. [α]_D¹⁷ = -6.3 deg [c 0.914, MeOH].

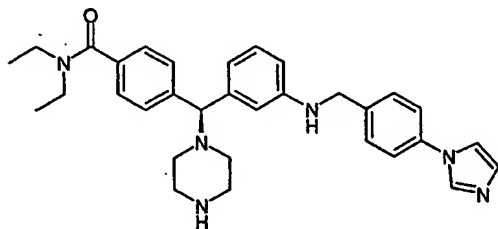
- 20 **COMPOUND 52:** *N,N*-diethyl-4-[(*S*)-1-piperazinyl[3-[[[4-(3-pyridinyl)phenyl]methyl]-amino]phenyl]methyl]benzamide



- 25 Using the same method as for COMPOUND 17 and using INTERMEDIATE 5a (205 mg, 0.44 mmol), 4-(3-pyridinyl)benzaldehyde (88.7 mg, 0.48 mmol), and decaborane (16.4 mg, 0.13 mmol) afforded COMPOUND 52 (266 mg, 61% yield) as its TFA salt. This material was lyophilized from CH₃CN/H₂O to produce a slightly yellow solid.

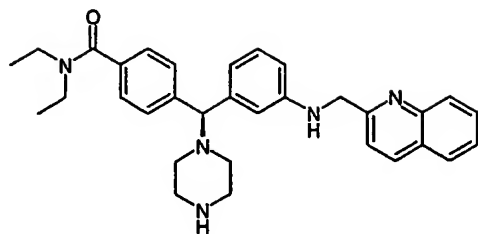
Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) δ 1.07 (br t, J = 6.9Hz, 3H), 1.20 (br t, J = 6.6Hz, 3H), 2.65 (br s, 4H), 3.21 (br s, 6H), 3.49 (br q, J = 7.2Hz, 2H), 4.38 (s, 1H), 4.47 (s, 2H), 6.66 (dd, J = 8.1, 1.5Hz, 1H), 6.85 (d, J = 7.8Hz, 1H), 6.89 (s, 1H), 7.10 (t, J = 7.8Hz, 1H), 7.25 (d, J = 8.2Hz, 2H), 7.49 (d, J = 8.2Hz, 2H), 7.55 (d, J = 8.2Hz, 2H), 7.76 (d, J = 8.4Hz, 2H), 8.08 (dd, J = 8.0, 5.7Hz, 1H), 8.79 (d, J = 4.9Hz, 1H), 8.82 (d, J = 8.2Hz, 1H), 9.14 (s, 1H). Found: C, 53.11; H, 4.81; N, 7.56. C₃₄H₃₉N₅O x 0.5 H₂O x 3.3 CF₃COOH has C, 53.06; H, 4.75; N, 7.62%. [α]_D¹⁸ = +10.7 deg [c 1.43, MeOH].

10 **COMPOUND 53:** *N,N*-diethyl-4-[(*S*)-[3-[[[4-(1*H*-imidazol-1-yl)phenyl]methyl]amino]-phenyl]-1-piperazinylmethyl]benzamide



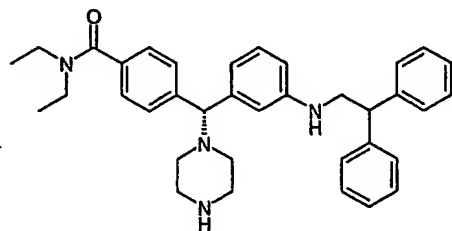
15 Using the same method as for COMPOUND 17 and using INTERMEDIATE 5a (206 mg, 0.44 mmol), 4-(1*H*-imidazol-1-yl)benzaldehyde (83.6 mg, 0.49 mmol), and decaborane (16.4 mg, 0.13 mmol) afforded COMPOUND 53 (181 mg, 42% yield) as its TFA salt. This material was lyophilized from CH₃CN/H₂O to produce a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) δ 1.09 (br t, J = 6.7Hz, 3H), 1.21 (br t, J = 6.7Hz, 3H), 2.63 (br s, 4H), 3.15-3.28 (m, 6H), 3.51 (q, J = 6.1Hz, 2H), 4.32 (s, 1H), 4.43 (s, 2H), 6.47-6.52 (m, 1H), 6.71-6.76 (m, 2H), 7.02 (t, J = 8.0Hz, 1H), 7.26 (d, J = 8.2Hz, 2H), 7.49 (d, J = 8.2Hz, 2H), 7.58 (d, J = 8.6Hz, 2H), 7.64 (d, J = 8.6Hz, 2H), 7.76 (s, 1H), 8.05 (s, 1H), 9.44 (s, 1H). Found: C, 51.44; H, 4.89; N, 9.63. C₃₂H₃₈N₆O x 1.2 H₂O x 3.0 CF₃COOH has C, 51.49; H, 4.94; N, 9.48%. [α]_D¹⁷ = -2.1 deg [c 0.872, MeOH].

COMPOUND 54: *N,N*-diethyl-4-[(*S*)-1-piperazinyl[3-[(2-quinolinylmethyl)amino]phenyl]-methyl]benzamide



Using the same method as for COMPOUND 17 and using INTERMEDIATE 5a (209 mg, 0.45 mmol), 2-quinolinecarboxaldehyde (77.6 mg, 0.49 mmol), and decaborane (16.4 mg, 0.13 mmol) afforded COMPOUND 54 (162 mg, 38% yield) as its TFA salt. This material was lyophilized from CH₃CN/H₂O to produce a yellow solid. Purity (HPLC): > 98%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) δ 1.07 (br t, J = 6.7Hz, 3H), 1.23 (br t, J = 6.6Hz, 3H), 2.59 (br s, 4H), 3.18 (br t, J = 4.4Hz, 6H), 3.52 (br q, J = 7.2Hz, 2H), 4.30 (s, 1H), 4.89 (s, 2H), 6.58 (dd, J = 7.9, 2.1Hz, 1H), 6.72 (s, 1H), 6.82 (d, J = 7.4Hz, 1H), 7.04-7.12 (m, 3H), 7.36 (d, J = 8.2Hz, 2H), 7.85-7.93 (m, 2H), 8.09 (td, J = 7.8, 1.2Hz, 1H), 8.22 (d, J = 8.2Hz, 1H), 8.27 (d, J = 8.4Hz, 1H), 8.87 (d, J = 8.6Hz, 1H). Found: C, 50.15; H, 4.57; N, 7.46. C₃₂H₃₇N₅O x 1.1 H₂O x 3.6 CF₃COOH has C, 50.20; H, 4.60; N, 7.47%. $[\alpha]_D^{17} = +20.8$ deg [c 0.726, MeOH].

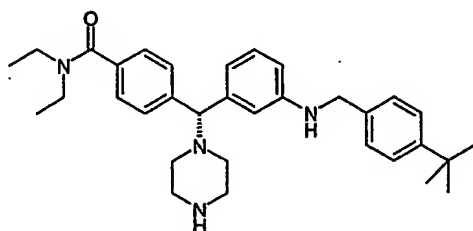
COMPOUND 55: 4-[(R)-[3-[(2,2-diphenylethyl)amino]phenyl]-1-piperazinylmethyl]-N,N-diethylbenzamide



Using the same method as for COMPOUND 17 and using INTERMEDIATE 5b (251 mg, 0.54 mmol), diphenylacetaldehyde (0.11 mL, 0.62 mmol), and decaborane (21.6 mg, 0.18 mmol) afforded COMPOUND 55 (186 mg, 39% yield) as its TFA salt. This

material was lyophilized from CH₃CN/H₂O to produce a white solid. Purity (HPLC): > 96%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) δ 1.06 (br t, J = 7.0Hz, 3H), 1.22 (br t, J = 7.0Hz, 3H), 2.65 (br s, 4H), 3.19-3.28 (m, 6H), 3.51 (br q, J = 7.2Hz, 2H), 3.79 (d, J = 7.6Hz, 2H), 4.24 (t, J = 7.6Hz, 1H), 4.38 (s, 1H),
 5 6.65 (dd, J = 8.1, 1.5Hz, 1H), 6.86 (s, 1H), 6.91 (d, J = 7.6Hz, 1H), 7.14 (t, J = 7.9Hz, 1H), 7.17-7.23 (m, 2H), 7.23-7.35 (m, 10H), 7.55 (d, J = 8.2Hz, 2H). Found: C, 56.89; H, 5.33; N, 6.32. C₃₆H₄₂N₄O x 0.7 H₂O x 2.8 CF₃COOH has C, 56.87; H, 5.30; N, 6.38%. [α]_D¹⁸ = +2.5 deg [c 1.023, MeOH].

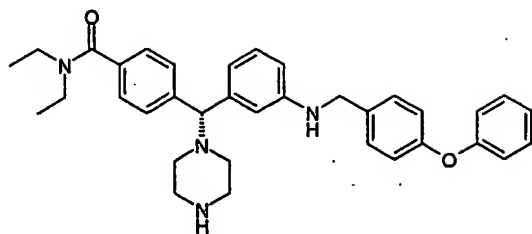
10 **COMPOUND 56:** 4-[(R)-[3-[[[4-(1,1-dimethylethyl)phenyl]methyl]amino]phenyl]-1-piperazinylmethyl]-N,N-diethylbenzamide



15

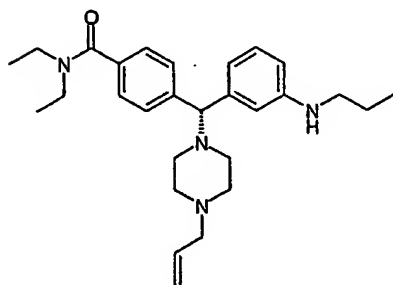
Using the same method as for COMPOUND 17 and using INTERMEDIATE 5b (254 mg, 0.54 mmol), 4-(1,1-dimethylethyl)benzaldehyde (0.10 mL, 0.60 mmol), and decaborane (21.6 mg, 0.18 mmol) afforded COMPOUND 56 (326 mg, 70% yield) as its TFA salt. This material was lyophilized from CH₃CN/H₂O to produce a white
 20 solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) δ 1.09 (br t, J = 6.7Hz, 3H), 1.22 (br t, J = 6.5Hz, 3H), 1.30 (s, 9H), 2.63 (br s, 4H), 3.21-3.27 (m, 6H), 3.52 (br q, J = 7.0Hz, 2H), 4.45 (s, 2H), 4.49 (s, 1H), 7.02 (d, J = 7.4Hz, 1H), 7.25-7.36 (m, 7H), 7.40 (d, J = 8.4Hz, 2H), 7.50 (d, J = 8.0Hz, 2H). Found: C, 49.54; H, 4.95; N, 5.67. C₃₃H₄₄N₄O x 0.7 H₂O x 4.2
 25 CF₃COOH has C, 49.52; H, 4.98; N, 5.58%. [α]_D¹⁹ = -9.23 deg [c 1.387, MeOH].

COMPOUND 57: N,N-diethyl-4-[(R)-[3-[[[4-phenoxyphenyl]methyl]amino]phenyl]-1-piperazinylmethyl]benzamide



Using the same method as for COMPOUND 17 and using INTERMEDIATE 5b (252 mg, 0.54 mmol), 4-phenoxybenzaldehyde (0.10 mL, 0.59 mmol), and decaborane (21.6 mg, 0.18 mmol) afforded COMPOUND 57 (269 mg, 56% yield) as its TFA salt. This material was lyophilized from CH₃CN/H₂O to produce a white solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) δ 1.07 (br t, J = 6.4Hz, 3H), 1.21 (br t, J = 6.4Hz, 3H), 2.60 (br s, 4H), 3.17-3.27 (m, 6H), 3.51 (br q, J = 6.6Hz, 2H), 4.42 (s, 1H), 4.44 (s, 2H), 6.90-7.00 (m, 5H), 7.07 (s, 1H), 7.09-7.17 (m, 2H), 7.24-7.38 (m, 7H), 7.46 (d, J = 8.0Hz, 2H). Found: C, 58.02; H, 5.40; N, 6.77. C₃₅H₄₀N₄O₂ x 0.5 H₂O x 2.3 CF₃COOH has C, 58.01; H, 5.32; N, 6.83%. [α]_D¹⁷ = -19.7 deg [c 1.340, MeOH].

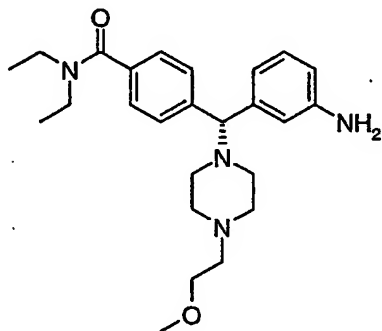
15 **COMPOUND 58:** *N,N*-diethyl-4-[(*R*)-[4-(2-propenyl)-1-piperazinyl][3-(propylamino)-phenyl]methyl]benzamide



20 A solution of COMPOUND 50 (54.8 mg, 0.13 mmol) in CH₃CN (4 mL) was cooled to 0 °C. Triethylamine (22.4 μL, 0.16 mmol) and allyl bromide (11.6 μL, 0.13 mmol) were added, and the reaction was allowed to warm to room temperature and stir for 2.5 hours. The reaction was then concentrated, and the residue was dissolved in

CH₂Cl₂ and washed twice with water. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 5% to 50% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 58 (54 mg, 51% yield) as a hygroscopic, white solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) δ 1.01 (t, J = 7.4Hz, 3H), 1.09 (br t, J = 6.6Hz, 3H), 1.22 (br t, J = 6.7Hz, 3H), 1.70 (sextet, J = 7.6Hz, 2H), 2.38 (br s, 2H), 3.02 (br s, 2H), 3.12-3.29 (m, 6H), 3.44-3.57 (m, 4H), 3.78 (d, J = 7.0Hz, 2H), 4.57 (s, 1H), 5.57-5.63 (m, 2H), 5.87-6.00 (m, 1H), 7.20 (dt, J = 7.4, 1.9Hz, 1H), 7.34 (d, J = 8.2Hz, 2H), 7.41-7.50 (m, 3H), 7.56 (d, J = 8.2Hz, 2H). Found: C, 51.99; H, 5.85; N, 7.25. C₂₈H₄₀N₄O x 0.8 H₂O x 2.7 CF₃COOH has C, 52.04; H, 5.79; N, 7.27%. [α]_D¹⁷ = -2.6 deg [c 1.03, MeOH].

COMPOUND 59: 4-[(*R*)-(3-aminophenyl)[4-(2-methoxyethyl)piperazin-1-yl]methyl]-*N,N*-diethylbenzamide

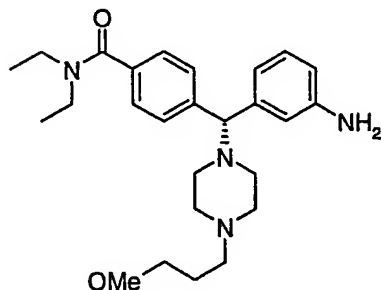


In a 5 mL microwave vial was added INTERMEDIATE 4b (1.7 g; 4.29 mmol) in DMF (4 mL) followed by potassium carbonate (1.19 g; 8.58 mmol) and 2-bromoethyl methyl ether (0.53 mL; 5.58 mmol). The reaction mixture was heated to 130°C for 15 minutes then was concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with saturated sodium bicarbonate followed by water. The organic phase was dried over anhydrous sodium sulphate, filtered and

concentrated under reduced pressure. Column chromatography eluting with 4% methanol in dichloromethane gave the desired product (0.9 g; 46% yield).

The above product was dissolved in a mixture of ethanol/THF/water/ NH_4Cl (2.1 mL) and iron (1.1 g; 19.8 mmol) was added. The reaction mixture was heated to 90°C for 5 hours, then was allowed to cool to room temperature, filtered on a celite pad and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatography eluting with 2% methanol and 1% NH_4OH in dichloromethane gave COMPOUND 59 (620 g; 74% yield). Purity (HPLC-215nm): > 99%; Optical purity (Chiral HPLC-215nm): > 99%. ^1H NMR (400 MHz, CD_3OD) δ 0.99 (t, $J = 7.52\text{Hz}$, 3H), 1.12 (t, $J = 6.54\text{Hz}$, 3H), 3.08-3.17 (br s, 3H), 3.18-3.23 (m, 6H), 3.29 (s, 3H), 3.26-3.32 (m, 3H), 3.44-3.51 (br s, 1H), 3.59-3.64 (m, 3H), 5.38 (s, 1H), 7.20 (d, $J = 7.42\text{Hz}$, 1H), 7.26 (d, $J = 8.01\text{Hz}$, 2H), 7.43 (t, $J = 7.81\text{Hz}$, 1H), 7.47-7.54 (br s, 3H), 7.59 (d, $J = 7.62\text{Hz}$, 1H). Found: C, 52.41; H, 7.54; N, 9.16. $\text{C}_{25}\text{H}_{36}\text{N}_4\text{O}_2 \times 3.2\text{HCl} \times 1.8\text{H}_2\text{O}$ has C, 52.34; H, 7.52; N, 9.77%. $[\alpha]_D^{17} = -7.0$ deg [c 0.50, MeOH].

COMPOUND 60: 4-[(R)-(3-aminophenyl)[4-(3-methoxypropyl)piperazin-1-yl)methyl]-N,N-diethylbenzamide



In a 5 mL microwave vial was added INTERMEDIATE 4b (1.7 g; 4.29 mmol) in DMF (3 mL) followed by potassium carbonate (1.19 g; 8.58 mmol) and 1-bromo-3-methoxypropane (0.85 g; 5.58 mmol). The reaction mixture was heated to 130°C for 15 minutes then was concentrated under reduced pressure. The residue was dissolved

in dichloromethane and washed with saturated sodium bicarbonate followed by water. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatography eluting with 3% methanol in dichloromethane gave the desired product (1.67 g; 83% yield).

5

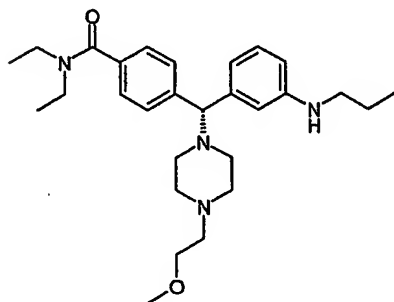
The above product was dissolved in a mixture of ethanol/THF/water/ NH_4Cl (3.5 mL) and iron (2.0 g; 35.6 mmol) was added. The reaction mixture was heated to 90°C for 5 hours, then was allowed to cool to room temperature, filtered on a celite pad and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and

10

washed with water. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatography eluting with 2% methanol and 1% NH_4OH in dichloromethane gave COMPOUND 60 (240 mg + 140 mg (93% pure); 24% yield). Purity (HPLC-215nm): > 99%; Optical purity (Chiral HPLC-215nm): > 99%. ^1H NMR (400 MHz, CD_3OD) δ 0.98 (t, J = 6.64Hz, 3H), 1.11 (t, J = 7.03Hz, 3H), 1.86-1.94 (m, 2H), 3.12-3.16 (br s, 3H), 3.17-3.21 (m, 9H), 3.22 (s, 3H), 3.41-3.46 (br s, 1H), 3.47-3.54 (br s, 3H), 5.38 (s, 1H), 7.21 (d, J = 7.03Hz, 1H), 7.27 (d, J = 7.62Hz, 2H), 7.44 (t, J = 7.91Hz, 1H), 7.52-7.57 (br s, 3H), 7.59-7.66 (br s, 1H). Found: C, 50.17; H, 7.48; N, 8.70. $\text{C}_{26}\text{H}_{38}\text{N}_4\text{O}_2 \times 4.0\text{HCl} \times 2.1\text{H}_2\text{O}$ has C, 50.18; H, 7.48; N, 9.00%. $[\alpha]_D^{17} = -7.1^\circ$ (c 0.52, MeOH).

20

COMPOUND 61: *N,N*-diethyl-4-[(*R*)-[4-(2-methoxyethyl)-1-piperazinyl][3-(propylamino)-phenyl]methyl]benzamide



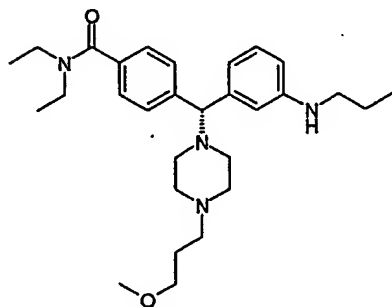
25

A solution of COMPOUND 59 (93.0 mg, 0.22 mmol), propionaldehyde (0.016 mL, 0.22 mmol) and decaborane (8.0 mg, 0.065 mmol) in methanol (5 mL) was stirred at

room temperature for 16 hours. The reaction was concentrated and then filtered through a short plug of silica gel using 4:1 CH₂Cl₂:MeOH as the eluent. The appropriate fractions were concentrated, and the residue was purified by reverse phase chromatography, eluting 5% to 50% acetonitrile in water containing 0.1%

- 5 trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 61 (90 mg, 51% yield) as a hygroscopic, slightly yellow solid. Purity (HPLC): > 95%; Optical purity (Chiral HPLC): > 93%; ¹H NMR (400MHz, CD₃OD) δ 1.01 (t, J = 7.5Hz, 3H), 1.09 (br t, J = 6.9Hz, 3H), 1.22 (br t, J = 6.6Hz, 3H), 1.70 (sextet, J = 7.6Hz, 2H), 2.44 (br s, 2H), 2.98 (br s, 2H), 3.19-3.28
10 (m, 5H), 3.34-3.40 (m, 3H), 3.38 (s, 3H), 3.52 (br q, J = 6.6Hz, 4H), 3.68-3.73 (m, 2H), 4.55 (s, 1H), 7.12-7.18 (m, 1H), 7.34 (d, J = 8.2Hz, 2H), 7.40-7.46 (m, 3H), 7.56 (d, J = 8.2Hz, 2H). Found: C, 50.65; H, 6.08; N, 7.02. C₂₈H₄₂N₄O₂ x 1.4 H₂O x 2.6 CF₃COOH has C, 50.58; H, 6.06; N, 7.11%. [α]_D¹⁸ = -0.6 deg [c 0.688, MeOH].

- 15 **COMPOUND 62:** *N,N*-diethyl-4-[(*R*)-[4-(3-methoxypropyl)-1-piperazinyl]][3-(propyl-amino)phenyl]methyl]benzamide

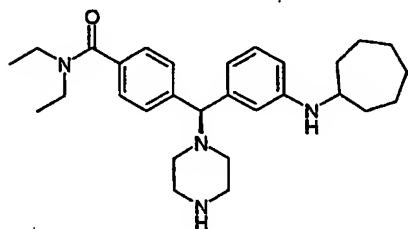


- 20 Using the same method as for COMPOUND 61 and using COMPOUND 60 (86.0 mg, 0.20 mmol), propionaldehyde (0.014 mL, 0.19 mmol) and decaborane (7.2 mg, 0.059 mmol) afforded COMPOUND 62 (89 mg, 55% yield) as its TFA salt. This material was lyophilized from CH₃CN/H₂O to produce a hygroscopic, slightly yellow solid. Purity (HPLC): > 97%; Optical purity (Chiral HPLC): > 93%; ¹H NMR (400MHz,
25 CD₃OD) δ 1.01 (t, J = 7.4Hz, 3H), 1.09 (br t, J = 6.6Hz, 3H), 1.22 (br t, J = 6.6Hz, 3H), 1.70 (sextet, J = 7.6Hz, 2H), 1.95-2.04 (m, 2H), 2.39 (br s, 2H), 3.01 (br s, 2H), 3.15-3.28 (m, 8H), 3.33 (s, 3H), 3.45-3.61 (m, 6H), 4.55 (s, 1H), 7.10-7.16 (m, 1H),

95

7.34 (d, $J = 8.2\text{Hz}$, 2H), 7.37-7.44 (m, 3H), 7.57 (d, $J = 8.0\text{Hz}$, 2H). Found: C, 53.22; H, 6.76; N, 7.48. $\text{C}_{29}\text{H}_{44}\text{N}_4\text{O}_2 \times 2.0 \text{ H}_2\text{O} \times 2.0 \text{ CF}_3\text{COOH}$ has C, 53.22; H, 6.77; N, 7.52%. $[\alpha]_D^{17} = -1.5 \text{ deg}$ [c 0.779, MeOH].

5 COMPOUND 63: 4-[(S)-[3-(cycloheptylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide

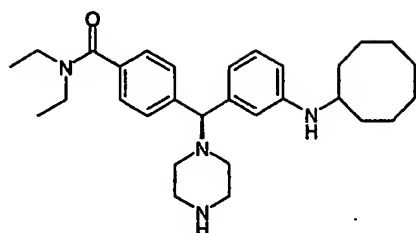


- 10 Synthesized according to the method used for COMPOUND 24 except that INTERMEDIATE 5a was used. The residue was purified by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 63 as a colourless solid. Purity (HPLC): > 99%;
- 15 Optical purity (Chiral HPLC): > 99%; ^1H NMR (400MHz, CD_3OD) 1.06 (t, $J = 6.54\text{Hz}$, 3H), 1.19 (t, $J = 6.64\text{Hz}$, 3H), 1.40-1.49 (m, 2H), 1.53-1.63 (m, 6H), 1.65-1.75 (m, 2H), 1.89-1.97 (m, 2H), 2.60-2.66 (m, 4H), 3.18-3.26 (m, 6H), 3.45-3.52 (m, 2H), 3.52-3.59 (m, 1H), 4.54 (s, 1H), 7.13 (dt, $J = 7.37, 1.68\text{Hz}$, 1H), 7.31 (d, $J = 8.40\text{Hz}$, 2H), 7.38-7.47 (m, 3H), 7.53 (d, $J = 8.20\text{Hz}$, 2H). Found: C, 52.27; H, 5.72; N, 6.94. $\text{C}_{29}\text{H}_{42}\text{N}_4\text{O} \times 0.4\text{H}_2\text{O} \times 2.9\text{TFA}$ has C, 52.21; H, 5.75; N, 7.00%. $[\alpha]_D^{20} = +8.69\text{deg}$ [c 0.61, MeOH].
- 20

COMPOUND 64: 4-[(S)-[3-(cyclooctylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide

25

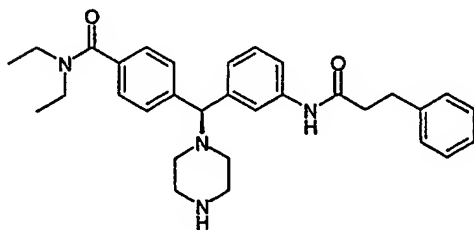
96



Synthesized according to the method used for COMPOUND 25 except that INTERMEDIATE 5a was used. The residue was purified by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 64 as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; $^1\text{H NMR}$ (400MHz, CD_3OD) 1.06 (t, J = 6.74Hz, 3H), 1.19 (t, J = 6.69Hz, 3H), 1.40-1.52 (m, 3H), 1.52-1.60 (m, 4H), 1.60-1.76 (m, 5H), 180-190 (m, 2H), 2.58-2.66 (m, 4H), 3.18-3.25 (m, 6H), 3.45-3.53 (m, 2H), 3.61-3.66 (m, 1H), 4.56 (s, 1H), 7.20 (ddd, J = 7.81, 2.15, 0.98Hz, 1H), 7.32 (d, J = 8.47Hz, 2H), 7.45 (t, J = 7.81Hz, 2H), 7.49 (br s, 1H), 7.51-7.55 (m, 3H). Found: C, 53.11; H, 6.01; N, 6.85. $\text{C}_{30}\text{H}_{44}\text{N}_4\text{O} \times 0.5\text{H}_2\text{O} \times 2.8\text{TFA}$ has C, 53.12; H, 5.00; N, 6.96%. $[\alpha]_{\text{D}}^{20} = +8.09\text{deg}$ [c 0.45, MeOH].

15

COMPOUND 65: N,N-diethyl-4-[(S)-{3-[(3-phenylpropanoyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide

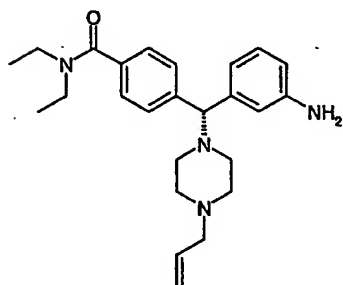


20

Synthesized according to the method used for COMPOUND 41 except that INTERMEDIATE 5a was used. The residue was purified by flash chromatography, eluting 25% methanol in dichloromethane, rising to 40% methanol in dichloromethane. The product was converted to the hydrochloride salt using 2M HCl

in diethyl ether to give COMPOUND 65 as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; ¹H NMR (400MHz, CD₃OD) 1.06 (t, J = 6.64Hz, 3H), 1.19 (t, J = 6.88Hz, 3H), 2.61 (t, J = 7.66Hz, 2H), 2.56-2.67 (m, 4H), 2.95 (t, J = 7.66Hz, 2H), 3.18-3.26 (m, 6H), 3.45-3.53 (m, 2H), 4.41 (s, 1H), 7.13-7.16 (m, 2H), 7.19-7.24 (m, 6H), 7.30 (d, J = 8.30Hz, 2H), 7.52 (d, J = 8.20Hz, 2H). Found: C, 61.14; H, 6.86; N, 9.10. C₃₁H₃₈N₄O₂ x 2.9HCl x 0.3H₂O has C, 61.06; H, 6.86; N, 9.19%. [α]_D²⁰ = -0.96deg [c 0.73, MeOH].

COMPOUND 66: 4-[(*R*)-(3-aminophenyl)[4-(2-propenyl)-1-piperazinyl]methyl]-*N,N*-diethyl- benzamide

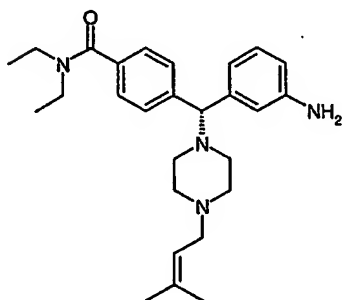


To a solution of INTERMEDIATE 4b (212 mg) in acetone (2 mL) in a microwave vial was added cesium carbonate (261 g; 1.5 eq) and allyl bromide (55 μL, 1.2 eq). The reaction was heated to 120°C for 5 minutes then was concentrated. The residue was dissolved in dichloromethane (20 mL) and washed with saturated aqueous sodium bicarbonate (20 mL) and water (20 mL). The organic layer was dried (MgSO₄), filtered and concentrated. Purification by flash chromatography, eluting 30% to 50% acetone in hexanes afforded the allylated product as a colourless foam (191 mg, 82% yield).

The above product was dissolved in a mixture of ethanol/tetrahydrofuran/water/saturated ammonium chloride (2 mL, 4:2:1:1 ratio) and placed in a microwave vial. To the solution was added iron (26 mg, 1.1eq) and the reaction was heated to 140°C for 10 minutes. Reaction was filtered through celite and dichloromethane/saturated sodium bicarbonate was added. The organic layer was

separated, dried (MgSO₄), filtered and concentrated. Purification by flash chromatography, eluting 30% to 50% acetone in hexanes afforded COMPOUND 66 as a colourless foam (101 mg, 53% yield). Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; (400MHz, CDCl₃) 1.06-1.15 (m, 3H), 1.16-1.27 (m, 3H), 2.30-2.60 (m, 6H), 3.00 (d, J = 6.32Hz, 2H), 3.19-3.32 (m, 2H), 3.48-3.57 (m, 2H), 4.11 (s, 1H), 5.11-5.20 (m, 2H), 5.85 (ddt, J = 17.16Hz, 10.25Hz, 6.57Hz, 1H), 6.52 (ddd, J = 7.82Hz, 2.25Hz, 1.07Hz, 1H), 6.72-6.75 (m, 1H), 6.78-6.82 (m, 1H), 7.05 (t, J = 7.64Hz, 1H), 7.27 (d, J = 8.21Hz, 2H), 7.43 (d, J = 8.20Hz, 2H). Found: C, 58.49; H, 7.24; N, 10.49. C₂₅H₃₄N₄O x 3.0 HCl, 0.2 C₄H₁₀O has C, 58.38; H, 7.41; N, 10.56 % [α]_D²⁰ = +6.09 deg [c 0.852, MeOH]

COMPOUND 67: 4-[(R)-(3-aminophenyl)[4-(3-methyl-2-butenyl)-1-piperazinyl]methyl]-N,N-diethyl-benzamide

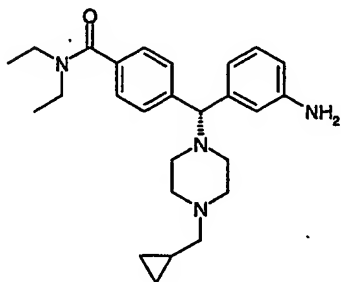


15

Synthesized according to the method of COMPOUND 66 except that 1-bromo-3-methyl but-2-ene was used in place of allyl bromide. From 206 mg of INTERMEDIATE 4b was generated 95 mg of COMPOUND 67. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; (400MHz, CD₃OD) 1.06 (m, 3H), 1.19 (m, 3H), 1.63 (s, 3H), 1.70 (s, 3H), 2.13-2.77 (m, 8H), 2.96 (d, J = 7.54Hz, 2H), 3.18-3.26 (m, 2H), 3.43-3.52 (m, 2H), 4.11 (s, 1H), 5.16-5.24 (m, 1H), 6.51 (d, J = 7.67Hz, 1H), 6.72 (d, J = 7.68Hz, 1H), 6.80 (s, 1H), 6.97 (t, J = 7.67Hz, 1H), 7.25 (d, J = 8.23Hz, 2H), 7.49 (d, J = 7.68Hz, 2H). Found: C, 56.55; H, 7.33; N, 9.59. C₂₇H₃₈N₄O x 3.8HCl, 0.1 H₂O, 0.1 C₁₀H₄O has C, 56.51; H, 7.44; N, 9.62 %. [α]_D²⁰ = +5.68 deg [c 0.545, MeOH]

25

COMPOUND 68: 4-[(*R*)-(3-aminophenyl)[4-(cyclopropylmethyl)-1-piperazinyl]methyl]-*N,N*-diethyl- benzamide



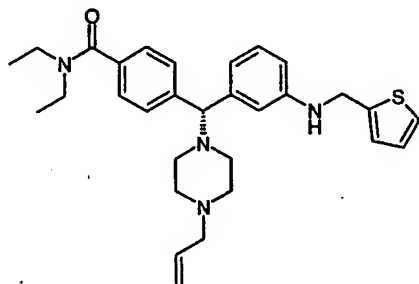
5

To a solution of INTERMEDIATE 4b (198 mg) in 1,2-dichloroethane was added cyclopropane carboxaldehyde (75 μ L, 2eq) and sodium triacetoxyborohydride (212 mg, 2eq). The reaction was stirred at room temperature for 20 hours than was diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate (10 mL). The organic layer was dried (MgSO_4), filtered and concentrated. The crude material was dissolved in a mixture of ethanol/tetrahydrofuran/water/saturated ammonium chloride (2 mL, 4:2:1:1 ratio) and placed in a microwave vial. To the solution was added iron and the reaction was heated to 140°C for 10 minutes. This procedure was repeated, with the addition of fresh iron until the reaction was completed. Reaction was filtered through celite and dichlormethane/saturated sodium bicarbonate was added. The organic layer was separated, dried (MgSO_4), filtered and concentrated. Purification by flash chromatography, eluting 70% acetone, 5% methanol, 3% concentrated ammonium hydroxide, 22% hexanes afforded COMPOUND 68 as a colourless foam (50 mg, 24% yield over two steps). Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; (400MHz, CD_3OD) 0.07-0.13 (m, 2H), 0.46-0.53 (m, 2H), 1.06 (t, $J = 6.56\text{Hz}$, 3H), 1.19 (t, $J = 6.84\text{Hz}$, 3H), 2.24 (d, $J = 6.70\text{Hz}$, 2H), 2.25-2.98 (m, 8H), 3.16-3.26 (m, 2H), 3.41-3.56 (m, 2H), 4.13 (s, 1H), 6.51 (ddd, $J = 8.01, 2.34, 0.98\text{Hz}$, 1H), 6.72 (dt, $J = 7.62, 1.17\text{Hz}$, 1H), 6.80 (t, $J = 1.95\text{Hz}$, 1H), 6.96 (t, $J = 7.81\text{Hz}$, 1H), 7.26 (d, $J = 8.39\text{Hz}$, 2H), 7.50 (d, $J = 8.01\text{Hz}$, 2H). Found: C, 56.28; H, 7.33; N, 9.49. $\text{C}_{26}\text{H}_{36}\text{N}_4\text{O} \times 3.8 \text{ HCl}$, 0.4 $\text{C}_4\text{H}_{10}\text{O}$ has C, 56.30; H, 7.50; N, 9.52 %. $[\alpha]_{\text{D}}^{20} = +5.61 \text{ deg}$ [c 0.641, MeOH].

25

100

COMPOUND 69: *N,N*-diethyl-4-[(*R*)-[4-(2-propenyl)-1-piperazinyl]][3-[(2-thienylmethyl)amino]phenyl]methyl]- benzamide



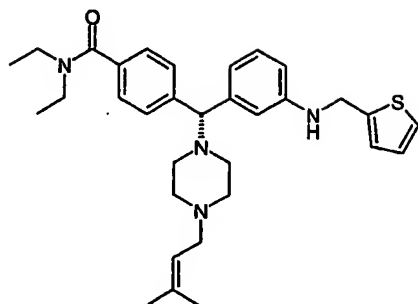
5

To a solution of COMPOUND 66 (80 mg) in 1,2-dichloroethane (5 mL) was added 2-thiophene carboxaldehyde (22 μ L, 1.2eq), sodium triacetoxyborohydride (83 mg, 2eq) and two drops of acetic acid. The reaction was stirred at room temperature for 20 hours than was diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate (10mL). The organic layer was dried (MgSO_4), filtered and concentrated. The residue was purified by reverse phase chromatography, eluting 10% to 45% acetonitrile in water containing 0.1% trifluoroacetic acid. The product was obtained as the trifluoroacetic acid salt and was lyophilized to give COMPOUND 69 (59 mg, 40% yield) as a colourless solid. Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; (400MHz, CD_3OD) 1.06 (t, $J = 6.74\text{Hz}$, 3H), 1.19 (t, $J = 6.74\text{Hz}$, 3H), 3.17-3.26 (m, 2H), 3.45-3.53 (m, 2H), 3.73 (d, $J = 7.42\text{Hz}$, 2H), 4.32 (s, 1H), 4.53 (s, 2H), 5.54-5.61 (m, 2H), 5.89 (ddt, $J = 17.27, 9.82, 7.26\text{Hz}$, 1H), 6.68 (ddd, $J = 7.94, 2.15, 0.78\text{Hz}$, 1H), 6.81-6.86 (m, 2H), 6.91 (dd, $J = 5.08, 3.51\text{Hz}$, 1H), 6.94-6.99 (m, 1H), 7.09 (t, $J = 7.81\text{Hz}$, 1H), 7.23-7.30 (m, 3H), 7.46 (d, $J = 8.21\text{Hz}$, 2H). Found: C, 52.32; H, 5.51; N, 7.16. $\text{C}_{30}\text{H}_{38}\text{N}_4\text{OS} \times 1.6\text{H}_2\text{O}, 2.3\text{CF}_3\text{COOH}$ has C, 52.35; H, 5.52; N, 7.06 %. $[\alpha]_D^{20} = -18.03 \text{ deg } [c 0.743, \text{MeOH}]$

25

COMPOUND 70: *N,N*-diethyl-4-[(*R*)-[4-(3-methyl-2-butenyl)-1-piperazinyl]][3-[(2-thienylmethyl)amino]phenyl]methyl]- benzamide

101

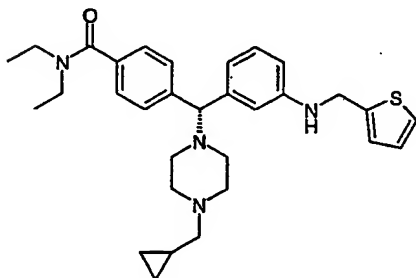


Synthesized using COMPOUND 67 and the method described for COMPOUND 69.

Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; (400MHz, CD₃OD)

- 5 1.06 (t, J = 6.61Hz, 3H), 1.19 (t, J = 6.61Hz, 3H), 1.76 (s, 3H), 1.82 (s, 3H), 2.11-2.27 (m, 2H), 2.89-3.14 (m, 4H), 3.14-3.26 (m, 2H), 3.32-3.42 (m, 2H), 3.45-3.54 (m, 2H), 3.71 (d, J = 7.93Hz, 2H), 4.27 (s, 1H), 4.47 (s, 2H), 5.22-5.29 (m, 1H), 6.56 (ddd, J = 7.94Hz, 2.37Hz, 1.02Hz, 1H), 6.68-6.71 (m, 1H), 6.77 (t, J = 2.20Hz, 1H), 6.91 (dd, J = 5.07Hz, 3.38Hz, 1H), 6.95-6.97 (m, 1H), 7.02 (t, J = 7.77Hz, 1H), 7.21 (dd, J = 5.07Hz, 1.19Hz, 1H), 7.26 (d, J = 8.05Hz, 1H), 7.47 (d, J = 8.12Hz, 2H). Found: C, 59.49; H, 6.40; N, 7.85. C₃₂H₄₂N₄O x 0.7H₂O x 1.4 CF₃COOH has C, 59.46; H, 6.42; N, 7.97%. [α]_D²⁰ = -20.30 deg [c 0.650, MeOH]
- 10

- COMPOUND 71: 4-[(R)-[4-(cyclopropylmethyl)-1-piperazinyl][3-[(2-thienylmethyl)amino]phenyl]methyl]-N,N-diethyl- benzamide
- 15



Synthesized using COMPOUND 68 and the method described for COMPOUND 69.

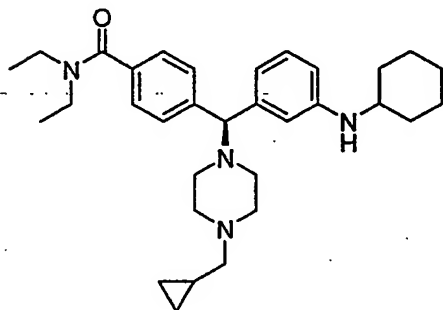
- 20 Purity (HPLC): > 99%; Optical purity (Chiral HPLC): > 99%; (400 MHz, CD₃OD) 0.39-0.44 (m, 2H), 0.72-0.78 (m, 2H), 1.04-1.10 (m, 1H), 1.07-1.11 (m, 3H), 1.22 (t, J = 6.99Hz, 3H), 2.20-2.36 (m, 2H), 2.91-3.08 (m, 2H), 3.04 (d, J = 7.49Hz, 2H), 3.06-

102

3.19 (m, 2H), 3.21-3.30 (m, 2H), 3.46-3.60 (m, 4H), 4.33 (s, 1H), 4.52 (s, 2H), 6.62 (dd, $J = 8.00, 2.44\text{Hz}$, 1H), 6.77 (d, $J = 7.58\text{Hz}$, 1H), 6.83 (t, $J = 1.81\text{Hz}$, 1H), 6.94 (dd, $J = 5.04, 3.53\text{Hz}$, 1H), 6.98-7.00 (m, 1H), 7.07 (t, $J = 7.80\text{Hz}$, 1H), 7.25 (dd, $J = 5.00, 122\text{Hz}$, 1H), 7.30 (d, $J = 8.17\text{Hz}$, 2H), 7.50 (d, $J = 8.16\text{Hz}$, 2H). Found: C, 53.58; H, 5.46; N, 7.10. $\text{C}_{31}\text{H}_{40}\text{N}_4\text{OS} \times 0.70\text{H}_2\text{O} \cdot 2.4\text{CF}_3\text{COOH}$ has C, 53.55; H, 5.50; N, 6.98%. $[\alpha]_{\text{D}}^{20} = -19.74 \text{ deg [c } 0.947, \text{MeOH}]$

COMPOUND 72: 4-[(S)-[3-(cyclohexylamino)phenyl][4-(cyclopropylmethyl)piperazin-1-yl]methyl]-N,N-diethylbenzamide

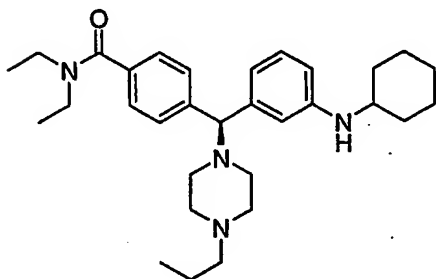
10



To a solution of COMPOUND 27 (250 mg; 0.56 mmol) in acetonitrile (8 mL) was added triethylamine (92.7 μL ; 0.67 mmol). The solution was cooled to 0°C than
15 bromomethylcyclopropane (53.5 μL ; 0.56 mmol) was added. Reaction mixture was stirred overnight then was concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with water. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatography eluting with 5% methanol in dichloromethane gave
20 COMPOUND 72 (229 g; 82% yield). Purity (HPLC-215nm): > 99%; Optical purity (Chiral HPLC-215nm): > 99%. ^1H NMR (400 MHz, CD_3OD) δ 0.34-0.40 (m, 2H), 0.65-0.71 (m, 2H), 0.99-1.04 (m, 3H), 1.14 (t, $J = 6.83\text{Hz}$, 3H), 1.30-1.35 (m, 6H), 1.61-1.64 (m, 1H), 1.75-1.78 (m, 2H), 1.85-1.90 (m, 2H), 2.46-2.54 (br s, 1H), 2.95-3.03 (br s, 6H), 3.10-3.18 (br s, 2H), 3.37-3.44 (br s, 5H), 3.54-3.60 (br s, 2H), 7.27-
25 2.31 (m, 3H), 7.50-7.53 (m, 3H), 7.64-7.68 (m, 2H). Found: C, 59.91; H, 8.10; N,

10.28. $C_{32}H_{46}N_4O \times 3.2HCl \times 1.1H_2O$ has C, 60.13; H, 8.10; N, 8.76%.
[α]_D¹⁶ = +12.4 deg [c 0.51, MeOH].

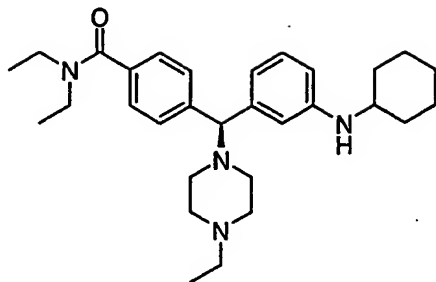
COMPOUND 73: 4-[(S)-[3-(cyclohexylamino)phenyl](4-propylpiperazin-1-yl)methyl]-N,N-diethylbenzamide



To a room temperature solution of propionaldehyde (40.6 μ L; 0.56 mmol) and
10 COMPOUND 27 (250 mg; 0.56 mmol) in 1,2-dichloroethane was added sodium
triacetoxy borohydride (380 mg; 1.79 mmol) and acetic acid (31.9 μ L; 0.56 mmol).
The reaction mixture was stirred overnight then was washed with saturated sodium
bicarbonate, followed by water. The organic phase was dried over anhydrous sodium
sulphate, filtered and concentrated under reduced pressure. Column chromatography
15 eluting with 5% methanol in dichloromethane gave COMPOUND 73 (169 g; 62%
yield). Purity (HPLC-215nm): > 99%; Optical purity (Chiral HPLC-215nm): > 99%.
¹H NMR (400 MHz; CD₃OD) δ 0.99 (t, J = 7.91 Hz, 2H), 1.10-1.16 (m, 3H), 1.28-1.33
(m, 4H), 1.61-1.65 (m, 4H), 1.75-1.79 (m, 4H), 1.83-1.90 (m, 4H), 2.97-3.01 (m, 2H),
3.13-3.15 (m, 2H), 3.17-3.28 (m, 8H), 3.42-3.46 (m, 2H), 3.52-3.54 (m, 1H), 5.08 (s,
20 1H) 7.24-7.29 (m, 3H), 7.48-7.51 (m, 3H), 7.55-7.57 (m, 1H), 7.62 (d, J = 7.42 Hz,
1H). Found: C, 56.59; H, 7.89; N, 8.25. $C_{31}H_{46}N_4O \times 4.3HCl \times 0.6H_2O$ has C, 56.56;
H, 7.89; N, 8.51%. [α]_D¹⁶ = +14.5 deg [c 0.50, MeOH].

COMPOUND 74: 4-[(S)-[3-(cyclohexylamino)phenyl](4-ethylpiperazin-1-yl)methyl]-N,N-diethylbenzamide

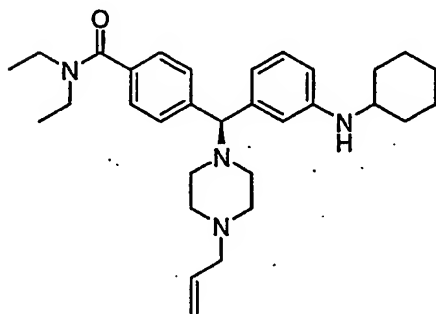
104



Synthesized using COMPOUND 27 (250 mg; 0.56 mmol) and the method described for COMPOUND 72. Obtained 163 g; 61% yield. Purity (HPLC-215nm): > 99%;
 5 Optical purity (Chiral HPLC-215nm): > 99%. ^1H NMR (400 MHz, CD_3OD) δ 0.80 (m, 1H), 1.19 (br s, 11H), 1.59 (m, 2H), 1.88 (br s, 5H), 3.14 (br s, 11H), 3.50 (br s, 4H), 4.11 (m, 1H), 7.31 (br s, 3H), 7.67 (br s, 5H). Found: C, 53.63; H, 7.55; N, 8.05. $\text{C}_{30}\text{H}_{44}\text{N}_4\text{O} \times 5.0\text{HCl} \times 0.7\text{H}_2\text{O}$ has C, 53.65; H, 7.56; N, 8.34%. $[\alpha]_D^{16} = +12.7$ deg [c 0.50, MeOH].

10

COMPOUND 75: 4-((S)-(4-allylpiperazin-1-yl)[3-(cyclohexylamino)phenyl]methyl)-N,N-diethylbenzamide



15

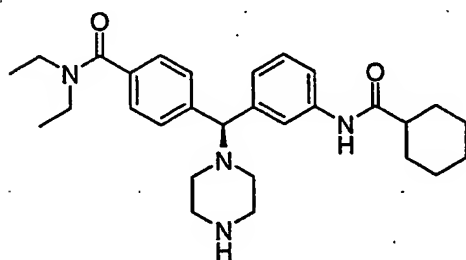
Synthesised using COMPOUND 27 (250 mg; 0.56 mmol) and the method described for COMPOUND 72. Obtained 240 g; 88% yield. Purity (HPLC-215nm): > 97%;
 Optical purity (Chiral HPLC-215nm): > 99%. ^1H NMR (400 MHz, CD_3OD) δ 1.00 (t, J = 6.44Hz, 3H), 1.13 (t, J = 7.32Hz, 3H), 1.22-1.40 (m, 5H), 1.58-1.63 (m, 1H),
 20 1.73-1.79 (m, 2H), 1.86-1.90 (m, 2H), 2.94-3.11 (br s, 2H), 3.12-3.19 (br s, 2H), 3.39-3.48 (br s, 7H), 3.75 (d, J = 6.83Hz, 2H), 5.49-5.53 (m, 3H), 5.54 (dd, J = 11.91,

105

10.54Hz, 1H), 5.87-5.91 (m, 2H), 7.27-7.33 (m, 3H), 7.49 (t, $J = 7.91\text{Hz}$, 1H), 7.55-7.59 (m, 2H), 7.67-7.72 (m, 2H). Found: C, 56.15; H, 7.58; N, 8.34. $\text{C}_{31}\text{H}_{44}\text{N}_4\text{O} \times 4.4\text{HCl} \times 0.8\text{H}_2\text{O}$ has C, 56.11; H, 7.60; N, 8.44%. $[\alpha]_D^{16} = +10.8\text{deg}$ [c 0.48, MeOH].

5

COMPOUND 76: 4-[(S)-{3-[(cyclohexylcarbonyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide



10

To a room temperature solution of INTERMEDIATE 5a (250 mg; 0.54 mmol) in dichloromethane (5 mL) were added triethylamine (0.15 mL; 1.08 mmol), DMAP (cat.) and cyclohexane carbonyl chloride (86 μL ; 0.64 mmol). The reaction mixture was stirred for 5 hours then more triethylamine (0.08 mL; 0.58 mmol) and DMAP (cat.) were added. The reaction mixture was stirred overnight then more cyclohexane carbonyl chloride (28 μL ; 0.21 mmol) was added. The reaction mixture stirred for 5 hours then was washed with two portions of saturated sodium bicarbonate. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatography eluting with 2% methanol in dichloromethane gave the desired product.

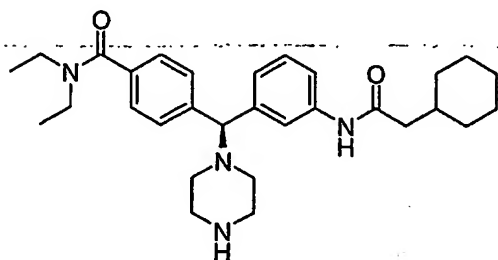
20

The above product was dissolved in dichloromethane (10 mL) and TFA (1.5 mL) was added. The reaction mixture was stirred for 3 hours then was washed with one portion of saturated sodium bicarbonate followed by one portion of brine. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatography eluting with 4.5% methanol in dichloromethane to 5% methanol in dichloromethane gave COMPOUND 76 (214 g; 83% yield for two steps). Purity (HPLC-215nm): > 99%; Optical purity (Chiral

25

HPLC-215nm): > 99%. ¹H NMR (400 MHz, CD₃OD) δ 0.98 (t, J = 7.52Hz, 3H), 1.11 (t, J = 7.62Hz, 3H), 1.16-1.34 (m, 3H), 1.37-1.42 (m, 2H), 1.58-1.64 (m, 1H), 1.70-1.78 (m, 4H), 2.18-2.31 (m, 1H), 3.10-3.17 (br s, 1H), 3.18-3.24 (m, 6H), 3.25-3.33 (br s, 3H), 3.48-3.52 (m, 2H), 5.08 (s, 1H), 7.19 (d, J = 5.86Hz, 2H), 7.26-7.31 (m, 3H), 7.57 (d, J = 7.62Hz, 2H), 7.84-7.87 (m, 1H). Found: C, 55.91; H, 6.99; N, 8.86. C₂₉H₄₀N₄O₂ x 4.0HCl has C, 55.95; H, 7.12; N, 9.00%. [α]_D¹⁷ = +8.3 deg [c 0.52, MeOH].

COMPOUND 77: 4-[(S)-{3-[(cyclohexylacetyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide



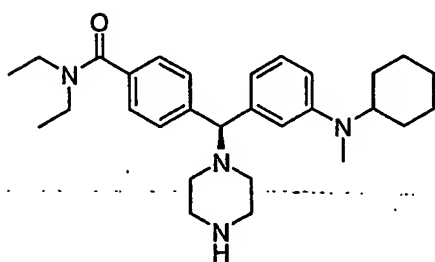
To a room temperature solution of INTERMEDIATE 5a (250 mg; 0.54 mmol) in DMF (5 mL) was added cyclohexyl acetic acid (92 mg; 0.65 mmol), DIPEA (0.38 mL; 2.16 mmol) and HATU (0.31 g; 0.81 mmol). The reaction mixture was stirred for 22 hours then was concentrated under reduced pressure. The residue was dissolved in dichloromethane, washed with sodium hydroxide (2N) then with HCl (1M). The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane (10 mL) and TFA (1.5 mL) was added. The reaction mixture was stirred for 4 hours then was washed with saturated sodium bicarbonate. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatography eluting with 5% methanol in dichloromethane gave COMPOUND 77 (242 g; 92% for two steps). Purity (HPLC-215nm): > 99%; Optical purity (Chiral HPLC-215nm): > 99%. ¹H NMR (400 MHz, CD₃OD) δ 0.87-0.93 (m, 2H), 0.98 (t, J = 7.13Hz, 3H), 1.08-1.14 (m, 3H), 1.20-1.23 (m, 2H), 1.52-1.71 (br s, 6H), 1.72-1.77 (m, 1H), 2.12 (d, J = 7.03Hz, 2H), 3.09-3.14 (m, 2H), 3.18-3.23 (m,

107

6H), 3.26-3.33 (br s, 3H), 3.48-3.52 (m, 1H), 5.08 (s, 1H), 7.20 (d, $J = 4.49\text{Hz}$, 2H), 7.24-7.31 (m, 3H), 7.57 (d, $J = 7.81\text{Hz}$, 2H), 7.83 (s, 1H). Found: C, 58.11; H, 8.99; N, 7.46. $\text{C}_{30}\text{H}_{42}\text{N}_4\text{O}_2 \times 0.4\text{HCl} \times 6.5\text{H}_2\text{O}$ has C, 57.90; H, 8.97; N, 9.00%. $[\alpha]_D^{17} = +4.6$ deg [c 0.46, MeOH].

5

COMPOUND 78: 4-[(S)-{3-[cyclohexyl(methyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide



10

To a room temperature solution of INTERMEDIATE 5a (300 mg; 0.64 mmol) in 1,2-dichloroethane (15 mL) were added cyclohexanone (0.20 mL; 1.93 mmol), sodium triacetoxy borohydride (0.43 g; 2.05 mmol) and acetic acid (37 μL ; 0.64 mmol). The reaction mixture was stirred for 6 hours then was washed with two portions of saturated sodium bicarbonate. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Column chromatography eluting with 4% methanol in dichloromethane gave the desired product.

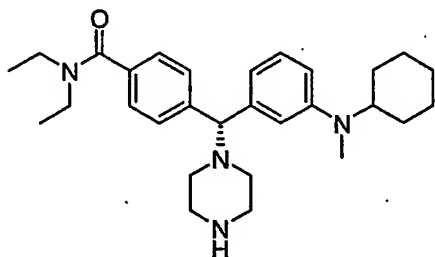
To a room temperature solution of the above product (320 mg; 0.58 mmol) in methanol (6 mL) was added formaldehyde (37% in H_2O) (130 μL ; 1.74 mmol). The reaction mixture was stirred for 30 minutes then decaborane (43 mg; 0.35 mmol) was added. The reaction mixture was stirred for 18 hours then was concentrated under reduced pressure. The residue was dissolved in dichloromethane then was washed with saturated sodium bicarbonate. The organic phase was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to give 296 mg of crude material. The crude material was dissolved in dichloromethane (10 mL) and TFA (1.5 mL) was added. The reaction mixture was stirred for 2.5 hours then saturated sodium bicarbonate was added. The organic phase was dried over

anhydrous sodium sulphate, filtered and concentrated under reduced pressure.

Column chromatography eluting with 5% methanol and 1% NH₄OH in dichloromethane gave COMPOUND 78 (211 g; 78% for two steps). Purity (HPLC-215nm): > 99%; Optical purity (Chiral HPLC-215nm): > 99%. ¹H NMR (400 MHz, CD₃OD) δ 0.98 (t, J = 7.13Hz, 3H), 1.11 (t, J = 7.52Hz, 3H), 1.21-1.32 (br s, 5H), 1.51-1.58 (m, 3H), 1.71-1.86 (br s, 2H), 3.11-3.18 (m, 5H), 3.22-3.33 (br s, 3H), 3.41-3.45 (m, 3H), 3.47-3.55 (br s, 2H), 4.48 (s, 3H), 5.08 (s, 1H), 7.27 (d, J = 8.40Hz, 3H), 7.49-7.52 (m, 3H), 7.56-7.67 (br s, 1H), 7.77-7.88 (br s, 1H). Found: C, 54.78; H, 7.71; N, 8.57. C₂₉H₄₂N₄O x 4.1HCl x 1.3H₂O has C, 54.80; H, 7.72; N, 8.81%.

10 $[\alpha]_D^{17} = +17.9$ deg [c 0.52, MeOH].

COMPOUND 79: 4-[(R)-{3-[cyclohexyl(methyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide



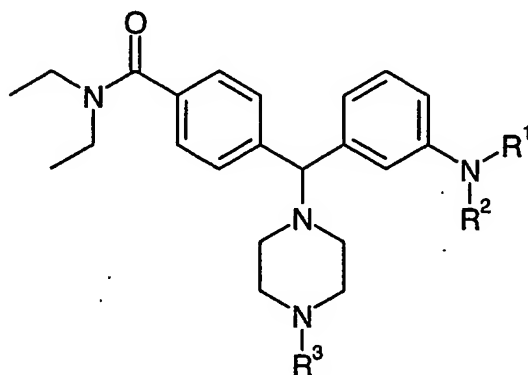
15

Synthesised using INTERMEDIATE 5b (250 mg; 0.54 mmol) and the method described for COMPOUND 78. Obtained 189 g; 79% yield for two steps. Purity (HPLC-215nm): > 99%; Optical purity (Chiral HPLC-215nm): > 99%. ¹H NMR (400 MHz, CD₃OD) δ 0.98 (t, J = 7.13Hz, 3H), 1.11 (t, J = 7.52Hz, 3H), 1.21-1.32 (br s, 5H), 1.51-1.58 (m, 3H), 1.71-1.86 (br s, 2H), 3.11-3.18 (m, 5H), 3.22-3.33 (br s, 3H), 3.41-3.45 (m, 3H), 3.47-3.55 (br s, 2H), 4.48 (s, 3H), 5.08 (s, 1H), 7.27 (d, J = 8.40Hz, 3H), 7.49-7.52 (m, 3H), 7.56-7.67 (br s, 1H), 7.77-7.88 (br s, 1H). Found: C, 53.87; H, 7.45; N, 8.39. C₂₉H₄₂N₄O x 4.8HCl x 0.5H₂O has C, 53.86; H, 7.45; N,

25 8.66%. $[\alpha]_D^{16} = -16.3$ deg [c 0.51, MeOH].

What is claimed is :

1. A compound of formula I, a pharmaceutically acceptable salt thereof:



5

I

wherein

- R¹ is selected from C₃₋₆alkyl, C₆₋₁₀aryl, C₂₋₉heteroaryl, C₆₋₁₀aryl-C₁₋₄alkyl, C₂₋₉heteroaryl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₄alkyl, R⁸-C(=O)-, R⁸-S(=O)₂-, R⁸-S(=O)-, R⁸-NHC(=O)-, R⁸-C(=S)- and R⁸-NH-C(=S)-, wherein R⁸ is selected from C₃₋₆alkyl, C₆₋₁₀aryl, C₂₋₉heteroaryl, C₆₋₁₀aryl-C₁₋₄alkyl, C₂₋₉heteroaryl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl, and C₃₋₁₀cycloalkyl-C₁₋₄alkyl, wherein said C₃₋₆alkyl, C₆₋₁₀aryl, C₂₋₉heteroaryl, C₆₋₁₀aryl-C₁₋₄alkyl, C₂₋₉heteroaryl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl, and C₃₋₁₀cycloalkyl-C₁₋₄alkyl used in defining R¹ and R⁸ are optionally substituted with one or more groups selected from -R, -NO₂, -OR, -Cl, -Br, -I, -F, -CF₃, -C(=O)R, -C(=O)OH, -NH₂, -SH, -NHR, -NR₂, -SR, -SO₃H, -SO₂R, -S(=O)R, -CN, -OH, -C(=O)OR, -C(=O)NR₂, -NRC(=O)R, and -NRC(=O)-OR, wherein R is, independently, selected from -H, C₁₋₆alkyl and phenyl;

- R² is selected from -H and C₁₋₆alkyl optionally substituted with one or more groups selected from halogen, -CF₃, -OH, C₁₋₃alkoxy, and halogen; and

R³ is selected from -H, C₁₋₆alkyl-O-C(=O)-, C₁₋₆alkyl, C₃₋₆cycloalkyl, and C₃₋₆cycloalkyl-C₁₋₄alkyl, wherein said C₁₋₆alkyl-O-C(=O)-, C₁₋₆alkyl, C₃₋₆cycloalkyl, and C₃₋₆cycloalkyl-C₁₋₄alkyl are optionally substituted with one or more groups selected from C₁₋₆alkyl, halogenated C₁₋₆alkyl, -NO₂, -CF₃, C₁₋₆alkoxy and halogen.

25

2. A compound according to claim 1, wherein
R¹ is selected from C₃₋₆alkyl, C₆₋₁₀aryl, C₂₋₆heteroaryl, C₆₋₁₀aryl-C₁₋₄alkyl, C₂₋₆heteroaryl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₄alkyl, wherein said C₃₋₆alkyl, C₆₋₁₀aryl, C₂₋₆heteroaryl, C₆₋₁₀aryl-C₁₋₄alkyl, C₂₋₆heteroaryl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl, C₃₋₁₀cycloalkyl-C₁₋₄alkyl are optionally substituted with one or more groups selected from C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy, and halogen;
R² is selected from -H and C₁₋₃alkyl; and
R³ is selected from -H and C₁₋₆alkyl-O-C(=O)-.
- 10 3. A compound according to claim 2,
wherein R¹ is R⁹-CH₂-, wherein R⁹ is selected from phenyl, pyridyl, thienyl, furyl, imidazolyl, triazolyl, pyrrolyl, thiazolyl, N-oxido-pyridyl, benzyl, pyridylmethyl, thienylmethyl, furylmethyl, imidazolylmethyl, triazolylmethyl, pyrrolylmethyl, thiazolylmethyl and N-oxido-pyridylmethyl, optionally substituted with one or more groups selected from C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy and halogen; and
R² and R³ are hydrogen.
- 20 4. A compound according to claim 3,
wherein R⁹ is selected from benzyl, phenyl, pyridyl, thienyl, furyl, imidazolyl, pyrrolyl and thiazolyl, optionally substituted with one or more groups selected from C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy, and halogen.
- 25 5. A compound according to claim 4, wherein
wherein R⁹ is selected from benzyl, phenyl, pyridyl, thienyl, furyl, imidazolyl, pyrrolyl and thiazolyl.
6. A compound according to claim 1, wherein
30 R¹ is selected from C₃₋₆alkyl, C₃₋₁₀cycloalkyl, and C₃₋₁₀cycloalkyl-C₁₋₄alkyl, wherein said C₃₋₆alkyl, C₃₋₁₀cycloalkyl, and C₃₋₁₀cycloalkyl-C₁₋₄alkyl are optionally

substituted with one or more groups selected from C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy, and halogen;

R² is -H or C₁₋₃alkyl; and

R³ is -H, C₁₋₆alkyl, C₃₋₆cycloalkyl, and C₃₋₆cycloalkyl-C₁₋₄alkyl, wherein said
5 C₁₋₆alkyl, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-C₁₋₄alkyl are optionally substituted with one or more groups selected from C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy, and halogen.

7. A compound according to claim 6, wherein

10 R¹ is selected from 1-propyl, 2-propyl, 1-butyl, 2-butyl, t-butyl, 2-methyl-1-propyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and cyclononyl;

R² is selected from -H, methyl, ethyl, 1-propyl and 2-propyl; and

R³ is selected from -H, methyl, ethyl, allyl, 3,3-dimethyl-allyl, cyclopropylmethyl, 2-methoxy-ethyl, and 3-methoxy-1-propyl.

15

8. A compound according to claim 1, wherein

R¹ is selected from R⁸-C(=O)-, R⁸-S(=O)₂-, R⁸-S(=O)-, R⁸-NHC(=O)-, R⁸-C(=S)- and R⁸-NH-C(=S)-, wherein R⁸ is selected from C₃₋₆alkyl, C₆₋₁₀aryl, C₂₋₆heteroaryl, C₆₋₁₀aryl-C₁₋₄alkyl, C₂₋₆heteroaryl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl, and C₃₋₁₀cycloalkyl-C₁₋₄alkyl; wherein said C₃₋₆alkyl, C₆₋₁₀aryl, C₂₋₆heteroaryl, C₆₋₁₀aryl-C₁₋₄alkyl, C₂₋₆heteroaryl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl, and C₃₋₁₀cycloalkyl-C₁₋₄alkyl are
20 optionally substituted with C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy, and halogen;

R² is -H; and

25 R³ is selected from -H and C₁₋₆alkyl-O-C(=O)-.

9. A compound according to claim 8, wherein

R⁸ is selected from phenyl, benzyl, phenethyl and cyclohexyl, wherein said phenyl, benzyl, phenethyl and cyclohexyl are optionally substituted with one or more
30 groups selected from methyl, methoxy and halogen.

10. A compound according to claim 1, wherein the compound is selected from:

- N,N-diethyl-4-((S)piperazin-1-yl{3-[(1,3-thiazol-2-ylmethyl)amino]phenyl}methyl)benzamide;
N,N-diethyl-4-((R)-piperazin-1-yl{3-[(1,3-thiazol-2-ylmethyl)amino]phenyl}methyl)benzamide;
5 4-[(S)-[3-(benzylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide;
N,N-diethyl-4-((R)-piperazin-1-yl{3-[(thien-2-ylmethyl)amino]phenyl}methyl)benzamide;
N,N-diethyl-4-((S)-piperazin-1-yl{3-[(thien-2-ylmethyl)amino]phenyl}methyl)benzamide;
10 4-[(R)-[3-(benzylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide;
N,N-diethyl-4-[(S)-{3-[(2-furylmethyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
4-[(R)-[3-(benzylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide;
N,N-diethyl-4-[(R)-{3-[(2-furylmethyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
15 N,N-diethyl-4-((R)-piperazin-1-yl{3-[(thien-3-ylmethyl)amino]phenyl}methyl)benzamide;
N,N-diethyl-4-((S)-piperazin-1-yl{3-[(thien-3-ylmethyl)amino]phenyl}methyl)benzamide;
20 N,N-diethyl-4-[(R)-{3-[(3-furylmethyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
N,N-diethyl-4-[(R)-{3-[(2-phenylethyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
4-[(R)-{3-[(cyclohexylmethyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;
25 N,N-diethyl-4-[(R)-piperazin-1-yl{3-[[4-trifluoromethyl]benzyl]amino}phenyl)methyl]benzamide;
4-[(R)-{3-[(cyclopentylmethyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;
30 4-[(S)-{3-[(cyclohexylmethyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;

- 4-[(R)-{3-[(cyclohex-1-en-1-ylmethyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;
- N,N-diethyl-4-[(S)-{3-[methyl(phenyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
- 5 N,N-diethyl-4-[(S)-{3-[ethyl(phenyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
- N,N-diethyl-4-[(R)-{3-[methyl(phenyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
- N,N-diethyl-4-[(R)-{3-[ethyl(phenyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
- 10 4-[(R)-{3-[(cyclohexylmethyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;
- 4-[(R)-[3-(cyclopentylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide;
- 4-[(R)-[3-(cycloheptylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide;
- 15 4-[(R)-[3-(cyclooctylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide;
- 4-[(R)-[3-(cyclononylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide;
- 4-[(S)-[3-(cyclohexylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide;
- N,N-diethyl-4-[(R)-{3-[(4-methylphenyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
- 20 N,N-diethyl-4-[(S)-{3-[(4-methylphenyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
- 4-[(R)-{3-[(3-chlorophenyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;
- 4-[(S)-{3-[(3-chlorophenyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;
- 25 4-[(R)-{3-[(2-fluorophenyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;
- 4-[(S)-{3-[(2-fluorophenyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;
- 30 4-[(R)-[3-(benzoylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide;
- N,N-diethyl-4-[(R)-{3-[(phenylacetyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;

- 4-[(S)-[3-(benzoylamino)phenyl](piperazin-1-yl)methyl]-N,N-diethylbenzamide;
N,N-diethyl-4-[(S)-{3-[(phenylacetyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
N,N-diethyl-4-[(R)-{3-[(2-methyl-2-phenylpropanoyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
5 N,N-diethyl-4-[(R)-(3-{[(3-fluorophenyl)acetyl]amino}phenyl)(piperazin-1-yl)methyl]benzamide;
4-[(R)-{3-[(cyclohexylacetyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;
10 N,N-diethyl-4-[(R)-{3-[(3-phenylpropanoyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
4-[(R)-{3-[(cyclohexylcarbonyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;
N,N-diethyl-4-[(R)-{3-[(phenylsulfonyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
15 4-[(R)-{3-[(benzylsulfonyl)amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;
N,N-diethyl-4-[(S)-{3-[(phenylsulfonyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
20 4-[(R)-{3-[(anilino)carbonyl]amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;
4-[(R)-{3-[(anilino)carbonothioyl]amino]phenyl}(piperazin-1-yl)methyl]-N,N-diethylbenzamide;
N,N-diethyl-4-[(S)-1-piperazinyl[3-(propylamino)phenyl]methyl]benzamide;
25 4-[(S)-[3-(dipropylamino)phenyl]-1-piperazinylmethyl]-N,N-diethylbenzamide;
N,N-diethyl-4-[(R)-1-piperazinyl[3-(propylamino)phenyl]methyl]benzamide;
4-[(R)-[3-(dipropylamino)phenyl]-1-piperazinylmethyl]-N,N-diethylbenzamide;
N,N-diethyl-4-[(S)-1-piperazinyl[3-[[[4-(3-pyridinyl)phenyl]methyl]-amino]phenyl]methyl]benzamide;
30 N,N-diethyl-4-[(S)-[3-[[[4-(1H-imidazol-1-yl)phenyl]methyl]amino]-phenyl]-1-piperazinylmethyl]benzamide;

- N,N*-diethyl-4-[(*S*)-1-piperazinyl[3-[(2-quinolinylmethyl)amino]phenyl]-methyl]benzamide;
- 4-[(*R*)-[3-[(2,2-diphenylethyl)amino]phenyl]-1-piperazinylmethyl]-*N,N*-diethylbenzamide;
- 5 4-[(*R*)-[3-[[4-(1,1-dimethylethyl)phenyl]methyl]amino]phenyl]-1-piperazinylmethyl]-*N,N*-diethylbenzamide;
- N,N*-diethyl-4-[(*R*)-[3-[(4-phenoxyphenyl)methyl]amino]phenyl]-1-piperazinylmethyl]benzamide;
- N,N*-diethyl-4-[(*R*)-[4-(2-propenyl)-1-piperazinyl][3-(propylamino)-phenyl]methyl]benzamide;
- 10 4-[(*R*)-(3-aminophenyl)[4-(2-methoxyethyl)piperazin-1-yl]methyl]-*N,N*-diethylbenzamide;
- 4-[(*R*)-(3-aminophenyl)[4-(3-methoxypropyl)piperazin-1-yl]methyl]-*N,N*-diethylbenzamide;
- 15 *N,N*-diethyl-4-[(*R*)-[4-(2-methoxyethyl)-1-piperazinyl][3-(propylamino)-phenyl]methyl]benzamide;
- N,N*-diethyl-4-[(*R*)-[4-(3-methoxypropyl)-1-piperazinyl][3-(propylamino)phenyl]methyl]benzamide;
- 4-[(*S*)-[3-(cycloheptylamino)phenyl](piperazin-1-yl)methyl]-*N,N*-diethylbenzamide;
- 20 4-[(*S*)-[3-(cyclooctylamino)phenyl](piperazin-1-yl)methyl]-*N,N*-diethylbenzamide;
- N,N*-diethyl-4-[(*S*)-{3-[(3-phenylpropanoyl)amino]phenyl}(piperazin-1-yl)methyl]benzamide;
- 4-[(*R*)-(3-aminophenyl)[4-(2-propenyl)-1-piperazinyl]methyl]-*N,N*-diethylbenzamide;
- 25 4-[(*R*)-(3-aminophenyl)[4-(3-methyl-2-butenyl)-1-piperazinyl]methyl]-*N,N*-diethylbenzamide;
- 4-[(*R*)-(3-aminophenyl)[4-(cyclopropylmethyl)-1-piperazinyl]methyl]-*N,N*-diethylbenzamide;
- N,N*-diethyl-4-[(*R*)-[4-(2-propenyl)-1-piperazinyl][3-[(2-thienylmethyl)amino]phenyl]methyl]-benzamide;
- 30 *N,N*-diethyl-4-[(*R*)-[4-(3-methyl-2-butenyl)-1-piperazinyl][3-[(2-thienylmethyl)amino]phenyl]methyl]-benzamide;

4-[(*R*)-[4-(cyclopropylmethyl)-1-piperazinyl][3-[(2-thienylmethyl)amino]phenyl]methyl]-*N,N*-diethyl-benzamide;
4-[(*S*)-[3-(cyclohexylamino)phenyl][4-(cyclopropylmethyl)piperazin-1-yl]methyl]-*N,N*-diethylbenzamide;
5 4-[(*S*)-[3-(cyclohexylamino)phenyl](4-propylpiperazin-1-yl)methyl]-*N,N*-diethylbenzamide;
4-[(*S*)-[3-(cyclohexylamino)phenyl](4-ethylpiperazin-1-yl)methyl]-*N,N*-diethylbenzamide;
4-[(*S*)-(4-allylpiperazin-1-yl)[3-(cyclohexylamino)phenyl]methyl]-*N,N*-
10 diethylbenzamide;
4-[(*S*)-{3-[(cyclohexylcarbonyl)amino]phenyl}(piperazin-1-yl)methyl]-*N,N*-diethylbenzamide;
4-[(*S*)-{3-[(cyclohexylacetyl)amino]phenyl}(piperazin-1-yl)methyl]-*N,N*-diethylbenzamide;
15 4-[(*S*)-{3-[cyclohexyl(methyl)amino]phenyl}(piperazin-1-yl)methyl]-*N,N*-diethylbenzamide;
4-[(*R*)-{3-[cyclohexyl(methyl)amino]phenyl}(piperazin-1-yl)methyl]-*N,N*-diethylbenzamide;
enantiomers thereof; and pharmaceutically acceptable salts thereof.

20

11. A compound according to any one of claims 1-10 for use as a medicament.

12. The use of a compound according to any one of claims 1-10 in the manufacture of a medicament for the therapy of pain, anxiety or functional
25 gastrointestinal disorders.

13. A pharmaceutical composition comprising a compound according to any one of claims 1-10 and a pharmaceutically acceptable carrier.

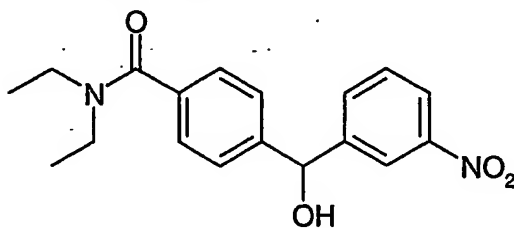
30 14. A method for the therapy of pain in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-10.

15. A method for the therapy of functional gastrointestinal disorders in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of
5 claims 1-10.

16. A method for the therapy of anxiety in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-10.

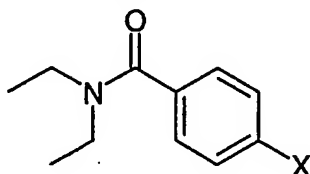
10

17. A process for preparing a compound of formula II, comprising:



II

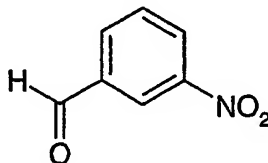
a) reacting a compound of formula III:



III

15

with a compound of formula IV



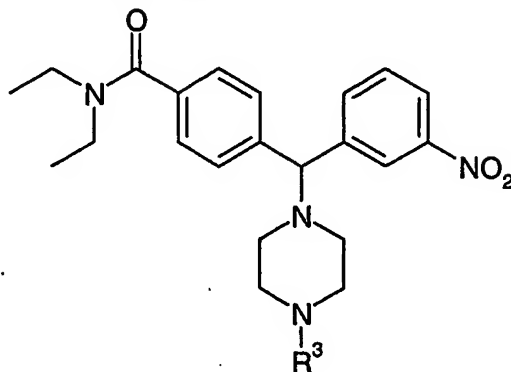
IV

20 in the presence of a base having a pKa of more than 15
wherein

X is a halogen.

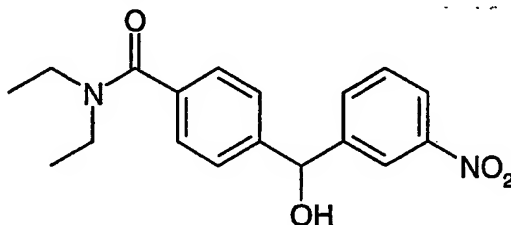
118

18. A process for preparing a compound of formula VI:



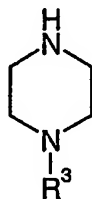
VI,

5 comprising: reacting a compound of formula II



II

with a compound of formula VII



VII

10

in the presence of SOX_2 to form the compound of formula VI,

wherein

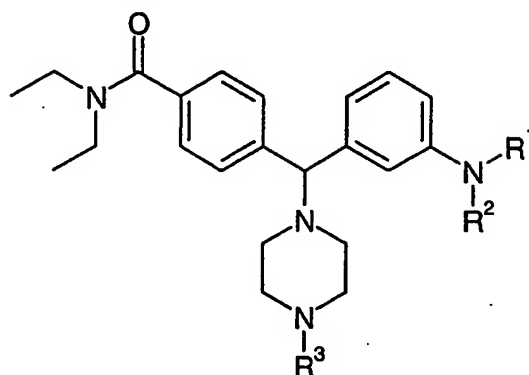
R^3 is selected from -H, C_{1-6} alkyl-O-C(=O)-, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl- C_{1-4} alkyl, wherein said C_{1-6} alkyl-O-C(=O)-, C_{1-6} alkyl, C_{3-6} cycloalkyl, and

15 C_{3-6} cycloalkyl- C_{1-4} alkyl are optionally substituted with one or more groups selected from C_{1-6} alkyl, halogenated C_{1-6} alkyl, $-\text{NO}_2$, $-\text{CF}_3$, C_{1-6} alkoxy and halogen; and

X is halogen.

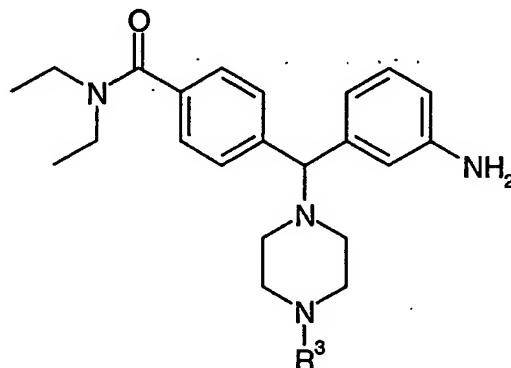
119

19. A process for preparing a compound of formula I,



I

comprising: reacting a compound of formula VIII,



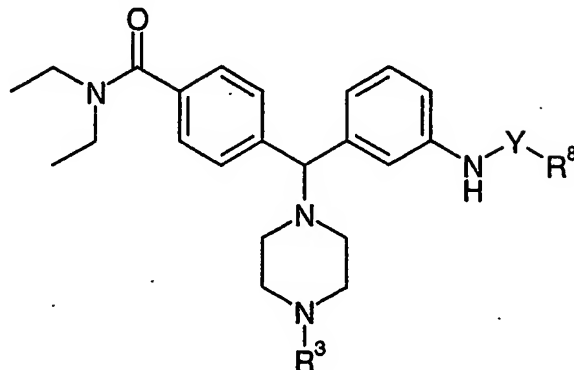
VIII

with R^9 -CHO in the presence of a reducing agent to form the compound of formula I:
wherein

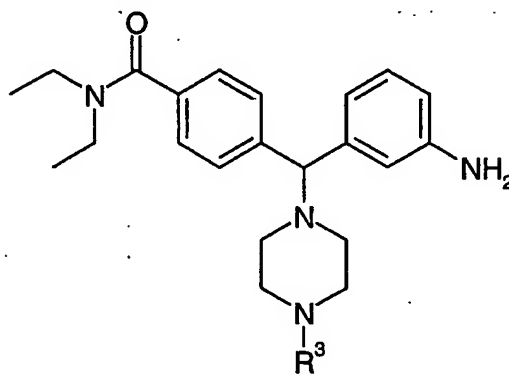
- R^1 is R^9 -CH₂-, wherein R^9 is selected from phenyl, pyridyl, thienyl, furyl,
 10 imidazolyl, triazolyl, pyrrolyl, thiazolyl, N-oxido-pyridyl, benzyl, pyridylmethyl,
 thienylmethyl, furylmethyl, imidazolylmethyl, triazolylmethyl, pyrrolylmethyl,
 thiazolylmethyl and N-oxido-pyridylmethyl, optionally substituted with one or more
 groups selected from C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy and
 halogen;
 15 R^2 is -H; and
 R^3 is selected from C₁₋₆alkyl-O-C(=O)-, C₁₋₆alkyl, C₃₋₆cycloalkyl, and C₃₋₆
 cycloalkyl-C₁₋₄alkyl, wherein said C₁₋₆alkyl-O-C(=O)-, C₁₋₆alkyl, C₃₋₆cycloalkyl, and
 C₃₋₆cycloalkyl-C₁₋₄alkyl are optionally substituted with one or more groups selected
 from C₁₋₆alkyl, halogenated C₁₋₆alkyl, -NO₂, -CF₃, C₁₋₆alkoxy and halogen.

120

20. A process for preparing a compound of formula IX,

IX

5 comprising: reacting a compound of formula VIII,



VIII

with R^8 -Y-X or R^8 -Y-O-Y- R^8 to form the compound of formula IX:

wherein

10 X is halogen;

Y is selected from $-C(=O)-$ and $-S(=O)_2-$;

R^8 is selected from C_{3-6} alkyl, C_{6-10} aryl, C_{2-6} heteroaryl, C_{6-10} aryl- C_{1-4} alkyl, C_{2-6} heteroaryl- C_{1-4} alkyl, C_{3-10} cycloalkyl, and C_{3-10} cycloalkyl- C_{1-4} alkyl; wherein said C_{3-6} alkyl, C_{6-10} aryl, C_{2-6} heteroaryl, C_{6-10} aryl- C_{1-4} alkyl, C_{2-6} heteroaryl- C_{1-4} alkyl, C_{3-10} cycloalkyl, and C_{3-10} cycloalkyl- C_{1-4} alkyl are optionally substituted with C_{1-4} alkyl, halogen, $-CF_3$, $-OH$, C_{1-3} alkoxy, phenoxy, and halogen; and

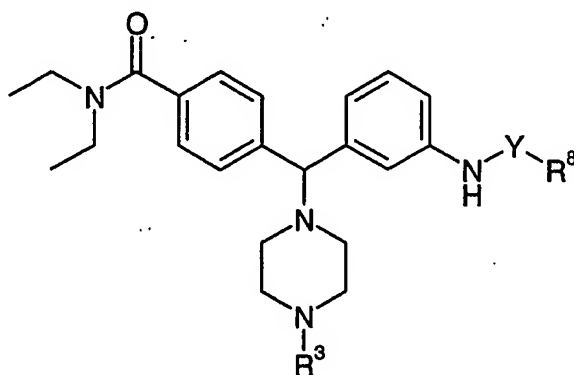
15

R^3 is selected from C_{1-6} alkyl-O-C(=O)-, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl- C_{1-4} alkyl, wherein said C_{1-6} alkyl-O-C(=O)-, C_{1-6} alkyl, C_{3-6} cycloalkyl,

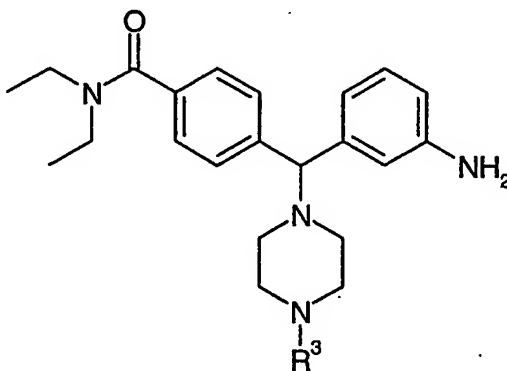
121

and C₃₋₆cycloalkyl-C₁₋₄alkyl are optionally substituted with one or more groups selected from C₁₋₆alkyl, halogenated C₁₋₆alkyl, -NO₂, -CF₃, C₁₋₆alkoxy and halogen.

21. A process for preparing a compound of formula IX,

**IX**

comprising: reacting a compound of formula VIII,

**VIII**

10 with R⁸-Z to form the compound of formula IX:

wherein

Z is selected from -NCO and -NCS;

Y is selected from -C(=O)NH- and -C(=S)NH-;

15 R⁸ is selected from C₃₋₆alkyl, C₆₋₁₀aryl, C₂₋₆heteroaryl, C₆₋₁₀aryl-C₁₋₄alkyl, C₂₋₆heteroaryl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl, and C₃₋₁₀cycloalkyl-C₁₋₄alkyl; wherein said C₃₋₆alkyl, C₆₋₁₀aryl, C₂₋₆heteroaryl, C₆₋₁₀aryl-C₁₋₄alkyl, C₂₋₆heteroaryl-C₁₋₄alkyl, C₃₋₁₀cycloalkyl, and C₃₋₁₀cycloalkyl-C₁₋₄alkyl are optionally substituted with C₁₋₄alkyl, halogen, -CF₃, -OH, C₁₋₃alkoxy, phenoxy, and halogen; and

R^3 is selected from C_{1-6} alkyl-O-C(=O)-, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl- C_{1-4} alkyl, wherein said C_{1-6} alkyl-O-C(=O)-, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl- C_{1-4} alkyl are optionally substituted with one or more groups selected from C_{1-6} alkyl, halogenated C_{1-6} alkyl, $-NO_2$, $-CF_3$, C_{1-6} alkoxy and halogen.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001706

Box No. II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **14-16**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001706

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Claims 14-16 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2003/001706

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 295/155, C07D 333/20, C07D 307/52, C07D 277/28, A61K 31/495,
A61K 31/496, A61P 25/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| X | WO 9315062 A1 (THE WELLCOME FOUNDATION LIMITED), 5 August 1993 (05.08.1993) -- | 1-21 |
| X | J. Med. Chem., Volume 43, 2000, Niklas Plobeck et al: "New Diarylmethylpiperazines as Potent and Selective Nonpeptidic delta Opioid Receptor Agonists with Increased In Vitro Metabolic Stability", page 3878 - page 3894, page 3882, scheme 9 -- | 18 |
| P,X | WO 02094794 A1 (ASTRAZENECA AB), 28 November 2002 (28.11.2002), claim 12 -- ----- | 18 |

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

B earlier application or patent but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

& document member of the same patent family

Date of the actual completion of the international search

20 February 2004

Date of mailing of the international search report

24-02-2004

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Solveig Gustavsson/Eö
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

Information on patent family members

24/12/2003

International application No.

PCT/SE 2003/001706

| | | | | | | |
|-------|----------|----|------------|----|--------------|------------|
| WO | 9315062 | A1 | 05/08/1993 | AT | 192197 T | 15/05/2000 |
| | | | | AT | 237597 T | 15/05/2003 |
| | | | | AU | 675928 B | 27/02/1997 |
| | | | | AU | 3457393 A | 01/09/1993 |
| | | | | CA | 2129046 A | 05/08/1993 |
| | | | | DE | 69230974 D,T | 19/10/2000 |
| | | | | DE | 69332882 D | 00/00/0000 |
| | | | | DK | 649414 T | 11/08/2003 |
| | | | | EP | 0649414 A,B | 26/04/1995 |
| | | | | SE | 0649414 T3 | |
| | | | | EP | 0650536 A,B | 03/05/1995 |
| | | | | GB | 9202238 D | 00/00/0000 |
| | | | | IL | 104582 A | 30/10/1998 |
| | | | | JP | 3109832 B | 20/11/2000 |
| | | | | JP | 3392415 B | 31/03/2003 |
| | | | | JP | 7501583 T | 16/02/1995 |
| | | | | JP | 7503247 T | 06/04/1995 |
| | | | | NZ | 246916 A | 27/08/1996 |
| | | | | PT | 649414 T | 30/09/2003 |
| | | | | US | 5492737 A | 20/02/1996 |
| | | | | US | 5574159 A | 12/11/1996 |
| | | | | US | 5658908 A | 19/08/1997 |
| | | | | US | 5681830 A | 28/10/1997 |
| | | | | US | 5854249 A | 29/12/1998 |
| | | | | US | 2002052007 A | 02/05/2002 |
| | | | | ZA | 9300717 A | 02/08/1994 |
| <hr/> | | | | | | |
| WO | 02094794 | A1 | 28/11/2002 | AU | 8040901 A | 13/03/2002 |
| | | | | SE | 0101772 D | 00/00/0000 |
| | | | | SE | 0103820 D | 00/00/0000 |
| <hr/> | | | | | | |

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant:

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.